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Archives of Internal Medicine

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THE FUNCTIONS AND INTEGRATION OF THE INTERCOSTAL MUSCLES *

C. F. HOOVER

CLEVELAND

The study of intercostal muscle function began with Galen, who believed the external intercostals to be expiratory and the internal intercostals inspiratory. This teaching was unquestioned until Vesalius, thirteen hundred years later, interpreted both external and internal muscles as having the same function. Thomas Willis, of Oxford, in 1673 for the first time interpreted the external muscles as inspiratory and the internal as purely expiratory. In 1748, Hamberger devised his famous model and the theory which has been quoted in all subsequent physiologic literature on respiration. Luciani says Hamberger's model "is an incomplete reproduction of costal excursion, but it served to elucidate the mechanism"—faint praise but quite sufficient for a scheme which misrepresents both costal excursion and intercostal function.

The only experimental confirmation of Hamberger's theory that is at all worthy of the problem is Martin and Hartwell's, an account of which was published in 1879. These experimenters isolated a pair of ribs by cutting all the intercostal structures which bound them above and below and with the sternum, but left intact the blood and nerve supply to the space between the two experimental ribs. The external intercostal muscle uniting the two ribs was then severed through its entire extent, and finally both ribs were cut so as to leave two segments of the ribs connected only by the internal intercostal muscles, the blood and nerve supply of which were left intact. Artificial respiration was employed and then, when automatic respiratory movements were set up after artificial respiration was suspended, the internal intercostal muscle was observed to contract during expiration only.

So far as this observation goes it is satisfactory, but it does not prove that the external intercostals are never expiratory, nor does it prove that the internal intercostals are never inspiratory. In this

* Read before the Experimental Section of the Cleveland Academy of Medicine, November, 1921.

experiment also no account is taken of the varying respiratory responses consequent on resistance to entrance and exit of air or varying amounts of the minute volume of air. Martin and Hartwell also failed to consider the varying effects on respiratory movements produced by different degrees and kinds of anesthesia and varying degrees of exhaustion of the respiratory innervation. Nor did these experimenters consider the integration of all the respiratory muscles in a normal animal.

With these considerations in mind, my experimental work has led me to formulate the following theses:

1. With tranquil respiration, only the external intercostals are activated during inspiration, and in expiration neither external nor internal intercostal muscle is employed.

2. With great hyperpnea, the external intercostals are activated during inspiration; and in expiration the internal intercostals only may be activated, but when the abdominal muscles are brought into use, either because of resistance to the exit of air or by intense hyperpnea, then the external muscles are synergically employed with the abdominal muscles. The external muscles are employed in expiration only when the abdominal muscles are requisitioned.

3. The internal intercostal muscles are employed in inspiration only when in the presence of hyperpnea there is added a resistance to the entrance of air.

4. The normal inspiratory and expiratory excursions of the ribs are determined not by the alternating actions of the two sets of intercostal muscles but by their integration with muscles that convert the results of their action into either an inspiratory or an expiratory effect. These auxiliary muscles are the scaleni and serratus posticus superior for inspiration, and the triangularis sterni and serratus posticus inferior for expiration.

Briefly stated, the external intercostal muscles are employed in inspiration in all respiratory conditions. There is a high threshold for their use in expiration, and this is passed only when they are activated synergically with the abdominal muscles. The internal are employed in expiration in hyperpnea, and have a threshold for expiratory use that is lower than that for the external intercostals. The internal intercostals are required in inspiration only in the combined presence of hyperpnea with resistance to the entrance of air. The highest threshold is for the inspiratory employment of the internal intercostal muscles, and then in descending order come the external intercostals in expiration, the internal intercostals in expiration, and finally the external muscles in inspiration.

PARALYSIS OF THE INTERCOSTAL MUSCLES.—The best example of the functional loss of the intercostal muscles that it has been my fortune to see was in a man about 50 years of age, who had had a severe attack of poliomyelitis when 25 years old. This man was in good health and suffered only the disability which resulted from poliomyelitis. He had a widely distributed and severe paresis and atrophy of the thoracoscapular and upper extremity muscles of both sides, and there was involvement of the muscles of the pelvic girth and both thighs and both legs. There was nowhere any evidence of sensory paresis. He had sufficient use of his arms and legs so that he was able to go about, though with considerable difficulty, and was able to take care of himself. Of the muscles employed in respiration, only the intercostals, triangularis sterni and serrati postici, superior and inferior, were involved, the scaleni, diaphragm and abdominal muscles being intact. All of the intercostal muscles were completely paralyzed with the exception of those going to the ninth, tenth, eleventh, and twelfth ribs of the right side. These four bottom ribs of the right side were the only ones that moved in response to intercostal muscles. That part of the right costal border formed by the ninth, ten, eleventh and twelfth ribs moved laterad in inspiration, and those ribs had also a normal bucket-handle movement. In inspiration the remaining portion of the right costal margin and the entire left costal margin moved toward the median line.

Estimated by his height and weight, his lungs should have had a vital capacity of 3,800 c.c., and without the aid of his intercostal muscles he did have a vital capacity of 3,200 c.c. This capacity was quite sufficient for respiratory purposes, but he could not expel air explosively from his lungs as required by a cough or sneeze. He had all the incentive to sneeze and completed the reflex procedure, but his sneeze was ineffective on account of the want of explosive expulsion of air. He had also observed that it was difficult for him to expel hard fecal matter. He said that a few years after his recovery from poliomyelitis he had an attack of bronchitis, which gave him much distress on account of his inability to expel mucus from his trachea, but he instinctively discovered that he could cough with considerable success if he placed his arms about his thorax and then threw himself on his side against the mattress of the bed. The man seemed to cough into instead of out of the lung. He could approximate his vocal cords with normal vigor, and the abdominal muscles were vigorous; from the strength of his laryngeal and abdominal muscles the observer would expect a vigorous cough, but he was unable to produce it. When the sides of his thorax were firmly supported by the hands of an attendant, he was able to cough like a normal person.

The ability to compress his lungs was tested by having him blow into a mercury manometer. In carrying out this test, in order to make sure that the patient did not employ his buccal muscles to raise the pressure in the manometer, he was required to blow through a tube in one nostril. He could raise the pressure just 50 mm., but with normal expiratory muscles he could have raised it 100 mm. It was quite apparent that the deficient compression of his lungs was due to paralysis of his intercostal muscles, which deprived him of circumferential constriction of the thorax.

The part played by the intercostal muscles in inspiring against resistance was shown when the patient was instructed at the end of a forced expiration to inspire with all his might through a tube (connected with a mercury manometer), which was inserted in a nostril while the mouth and other nostril were held shut. The highest column of mercury he could raise in this manner was 46 mm. In view of the fact that a normal person can inspire against a resistance that is 90 per cent. as great as the positive pressure he can raise within the lung, it is apparent that the loss in forceful inspiratory action was proportionately the same as the loss in power of compressing the lungs.

If we consider the pneumatics of the experiment, the basic reasons for his disability stand out with great clearness. There were at least 1,000 c.c. of residual air in his lung at the end of a forced expiration, and then he added 3,200 c.c. by the use of his diaphragm and scaleni. While this volume of air was contained in the lung, he blew into the manometer by contracting his abdominal muscles, which served to drive the diaphragm upward. By this effort the mercury manometer registered a pressure of 50 mm.; therefore, his lungs were compressed to $\frac{750}{800} \times 4200$, which equals 3,937 c.c. The diminution in volume of the 4200 c.c. under a pressure of 50 mm. of mercury equaled 263 c.c.

In this formula 750 = the barometric pressure which prevailed at the time;

800 = pressure to which the contained air in the lung was subjected by the muscular effort.

If, as a normal man should, he had been able to attain an intrapulmonic pressure of 100 mm. mercury, the 4,200 c.c. of air would have been compressed to a volume of 3,705. There would, therefore, have been a further diminution in volume of 222 c.c. for the rise in pressure from 50 to 100 mm. mercury. From the original estimate of this man's vital capacity, we assume that he was deprived of only 600 c.c. by paralysis of his intercostal muscles. Now, suppose in the act of blowing into the manometer he had been able to accomplish a completely normal expiratory excursion of his ribs, he would have further reduced the volume of air in his lungs by 600 c.c. Had his

intercostal muscles been sufficiently strong to accomplish this compression, he would have raised the pressure in the manometer to 193 mm. mercury—that is, 143 mm. higher than the 50 mm. he was able to attain. This is estimated according to the following formula:

$$\frac{750}{800 + x} \times 4{,}200 = 3{,}337.$$

In this formula, 750 = barometric pressure.

800 = mm. of mercury pressure which was actually produced by the patient's muscular effort.

x = the unknown added pressure (143 mm. mercury which would have been necessary to compress the air 600 c.c. less than the volume which was attained by the effort he actually employed. As shown above, this volume was 3,937).

4,200 = the original volume of air in the lung at prevailing barometric pressure.

This computation shows in an interesting way the physical basis for the man's disability to constrict his thorax for want of his intercostal muscles. He was able to raise his intrapulmonic pressure just half as high as if he possessed normally functioning intercostal muscles, but the vital capacity of his lungs was impaired only 15 per cent. of the normally expected amount.

The power of lowering air pressure in the lungs by inspiratory effort was also diminished in the same proportion as was the power of compression. The losses in power of circumferential constriction and of expansion were the same, which indicates that exactly the same musculature is employed in both, or at least that an equal loss for both processes is incurred by motor paralysis of all the intercostal muscles. Therefore, if it can be shown that both external and internal intercostals are employed in forced compression, the corollary follows that both sets of muscles are employed in forced expansion.

Loss of all intercostal function, as shown by the preceding discussion, leaves the patient in respiratory comfort with the loss of only between 15 and 20 per cent. of vital capacity. The major disability incurred by paralysis of all the intercostal muscles lies wholly within any effort that demands compression or distension of the lung against resistance.

The opportunity to examine the thoracic excursion of a man with normal cardiorespiratory function, with the exception of motor paralysis of the intercostal muscles, was a rare opportunity. I can find no other similar case in medical literature. The surprising

features of his disability were the slight loss of vital capacity and the great loss in the ability forcibly to compress and to distend the lungs. It is obvious that the slightness of the diminution in vital capacity was not due so much to the normally small share of the lost costal excursion in lung distension as to the abdominal muscles—which by their attachments to the entire costal borders and lower end of the sternum were able to pull the lower six pairs of ribs downward and toward the median line and to pull the sternum with its attached ribs in a downward direction—and also to the inspiratory aid of the scaleni, which will be considered later in the discussion.

CONTRIBUTION OF EACH GROUP TO VITAL CAPACITY.—In this relation it seemed desirable to learn about how much of the vital capacity may be lost when both the intercostal and abdominal muscles are paralyzed. Under such conditions the actual share of phrenic excursion in procuring vital capacity can be estimated, because in expiration the ribs cannot be drawn into a forced expiratory position by the abdominal muscles.

EXPERIMENT 1.—A vigorous dog, weighing 11 kilos, was used. Before the administration of ether there was given only ¼ grain morphin so that the respiratory center would be depressed as little as the operative conditions would allow. A tracheal cannula was inserted and connected with the reservoir of a Benedict apparatus that contained 75 per cent. oxygen and 25 per cent. carbon dioxid. This was done with the idea that if the animal were under light anesthesia he would exhibit nearly his whole vital capacity in the ensuing hyperpnea that would be demanded by rebreathing such a high percentage of carbon dioxid. As will be later shown, it was closely approximated.

In Figure 1, line A, is seen the tracing made on a drum revolving at the rate of 5 mm. per second. The time marker is in one-fifth second. The dog rebreathed into a Benedict apparatus with a clamp on the tubes leading to the canister. The largest excursion of the reservoir recorded a tidal air of 704 c.c. The spinal cord was then sectioned at the level of the top of the body of the first dorsal vertebra. The scaleni and diaphragm were the only respiratory muscles left intact; the intercostals, triangularis sterni, serrati postici and abdominal muscles being paralyzed. During inspiration the diaphragm had a large excursion, as shown by the inspiratory protrusions of the upper abdomen; both costal margins were drawn toward the median line and the lateral aspects of the thorax were slightly retracted. The tracheal cannula was reconnected with the Benedict reservoir within a few minutes after the spinal cord was sectioned. The tracing in line B, Figure 1, was then made on a drum slowly revolving at a rate of 1 mm. per second. The transitions from inspiration to expiration and vice versa are seen to be at first very prompt, and then gradually there developed a change in the automatic steering. The transition from expiration to inspiration remained the same, but there was a prolongation of the time between the end of inspiration and the end of expiration.

As seen in Figure 1, line A at x, before the cord was sectioned the duration of an inspiration was four-fifths second and of an expiration seven-fifths second. Lines C, D, E and F (Fig. 1) are tracings of the respiration after the cord was sectioned. The speed of the drum was 5 mm. per second, and the time marker registered in one-fifths of a second. At Y, line E, the duration of an inspiration was four-fifths second, but from the height of inspiration to the end of expiration was thirteen-fifths second. The diaphragm was held near the maximum point of excursion for nine-fifths second, and then it was

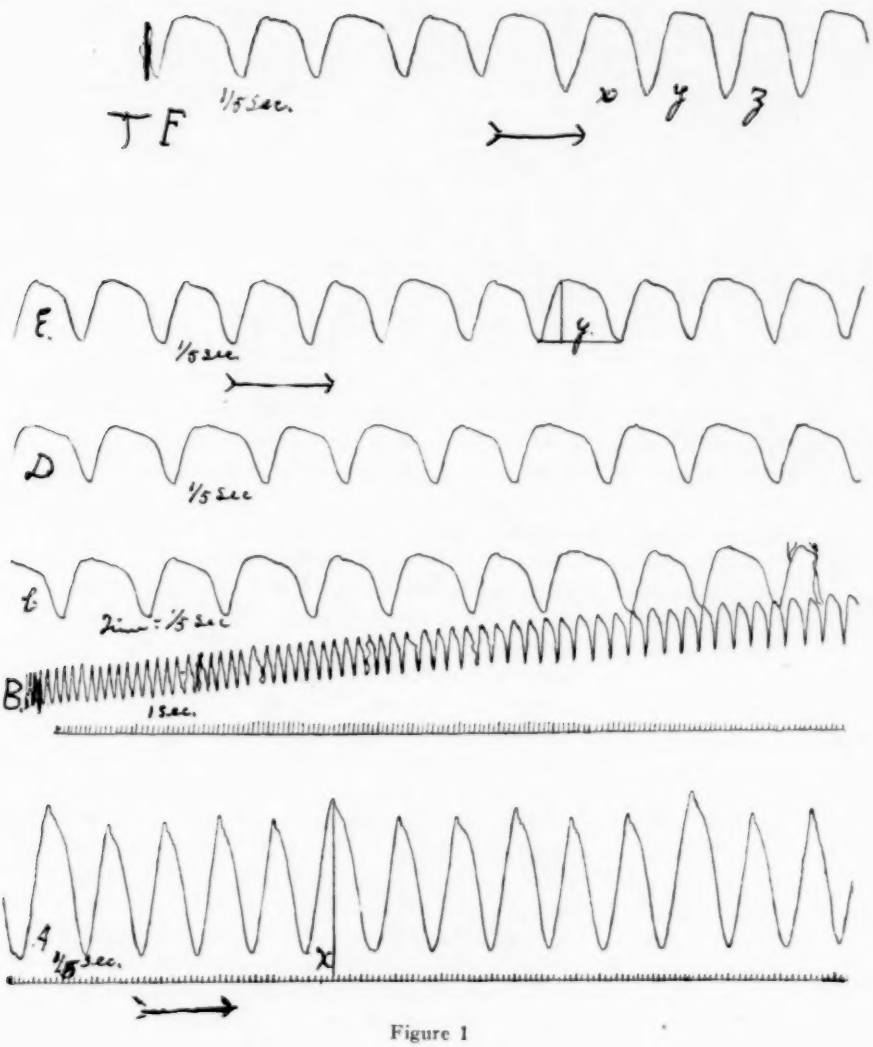

Figure 1

relaxed as the retractile lung expelled its contents in the remaining four-fifths second. After section of the cord the largest tidal air recorded was 308 c.c., which is only 43 per cent. of the tidal air procured before the intercostal system and abdominal muscles were paralyzed. Under these conditions 67 per cent. of the vital capacity was lost, whereas in the patient with paralyzed intercostals and intact abdominal muscles there was a loss of only 15 per cent. of the vital capacity.

An attempt was made to simulate the forced expiratory phase of the patient with paralyzed intercostals and active abdominal muscles by compressing the dog's abdomen with the palms of both hands and at the same time pulling in both costal margins by the finger tips (Fig. 1, line F at x, y, z). This procedure increased the tidal air from 308 to 440 c.c., which is 62 per cent. of the vital capacity under normal conditions. Of course this procedure did not adequately represent the function of normal abdominal muscles, but it indicates how the mechanism could be approximated. Cutting the cord slowed the respiratory rate from 24 to 16 per minute, but the slowing of the rate was due to the change in the automatic steering, which consisted in a delay of the transition from inspiration to expiration.

To determine (before the dog's cord was severed) how nearly the tidal air equaled the vital capacity, the pluck was removed and measurement was made of the volume of air that could be expressed from the lungs after they were given their maximum distension. This was found to be 1,012 c.c. If from this we substract 200 c.c. for residual air, there remain 812 c.c., which is only 94 c.c. in excess of the tidal air (708 c.c.) obtained when the animal was breathing the high percentage of carbon dioxid. When we consider the possible excess of distension obtained by blowing up the excised lungs above the maximum inspiratory distension during life, it is apparent that the 704 c.c. of tidal air closely approximated the dog's vital capacity when all the respiratory muscles were intact, and 308 c.c. the vital capacity after the intercostal system and abdominal muscles were paralyzed.

During the time the dog was breathing his maximum minute volume of air when the cord was intact, the abdominal muscles were vigorously contracted during expiration, and although the intrapleural pressure was not measured during that time, the fact that the abdominal muscles were vigorously contracted is good evidence that the pressure in the pleural cavity was raised above barometric pressure. The active vigor with which expiration is performed in such experiments depends on the depth of anesthesia and the state of exhaustion of the animal. When the intercostals alone are paralyzed, the abdominal muscles contribute to the vital capacity by their expiratory aid, as shown in the patient whose intercostals were paralyzed while the abdominal muscles were intact.

Experiment 2 was done to show how much of the vital capacity of an animal is sacrificed when the diaphragm is paralyzed and the scaleni, intercostals and abdominal muscles are intact.

EXPERIMENT 2.—A dog weighing 17 kilos was given ¼ grain morphin prior to ether anesthesia. After insertion of a tracheal cannula, the animal rebreathed into the Benedict reservoir containing 75 per cent. oxygen and 25 per cent. carbon dioxid. During this period of intense hyperpnea, the dog very vigorously contracted the abdominal muscles during expiration, so that we have good reason for saying he was employing his maximum expiratory and inspiratory efforts. The largest tidal air was 836 c.c. The phrenic nerves were then sectioned in the lower portion of the cervical region and rebreathing of a high percentage of carbon dioxid was resumed. During this period the outward movement of the costal margins was very greatly exaggerated, and in expiration the abdominal muscles were strongly contracted. The largest tidal air procured was 418 c.c.

An incision was then made in the abdomen and the leaves of the diaphragm were inspected. They were found to be paralyzed on both sides, but there was a vigorous contraction of the crura of the diaphragm, which evidently received some nerve supply from the cord below the origin of the phrenics. The active contraction of the crura drew the mid-portions of the diaphragm slightly downward and backward, and no doubt contributed somewhat to stabilizing the whole diaphragm, so that it did not ascend during inspiration when the intercostals were strongly activated.

The inability to get absolute paralysis of the entire diaphragm by sectioning the phrenic nerves makes the estimation of the diaphragm's contribution to vital capacity somewhat doubtful. The manner in which this dog's diaphragm behaved will not allow the assumption that all the share of the diaphragm in inspiration was eliminated. However, so far as our observations go, they indicate that paralysis of the intercostal muscles with preservation of the abdominal muscles reduces the vital capacity only about 15 per cent., whereas paralysis of the diaphragm which follows sectioning of the phrenic trunks reduces the vital capacity about 50 per cent.

To see how nearly the maximum tidal air of the animal represented his vital capacity, the intercostal spaces on both sides were freely opened and after the animal died the lungs were blown up to their maximum capacity in situ within the thorax, and then the escaping air was measured as the lungs passively contracted. The amount of air thus expelled from maximum distension to maximum contraction was 1,276 c.c. So it seems that 836 c.c. closely approximates the animal's vital capacity when we consider the residual air to have been about 300 c.c.

This experiment was done on three different animals. In one experiment there was very slight action of the pillars of the diaphragm after the phrenics were cut. In two animals that part of the diaphragm inserted on the vertebrae contracted with great vigor, but in all the animals that part of the diaphragm inserted laterally to the vertebrae and on the costal borders was completely paralyzed. This observation was confirmed by making an incision through the diaphragm so that the entire extent of the phrenic structure could be palpated between the thumb and fingers.

Experiment 3 was employed to give some conception of the ventilatory capacity of the intercostals when the diaphragm was paralyzed and the abdominal muscles eliminated by cutting away their attachments to the costal borders.

EXPERIMENT 3.—After a preliminary dose of ¼ grain morphin, a tracheotomy tube was introduced into the trachea of a dog under ether anesthesia and connected with a Benedict reservoir containing 20 per cent. carbon dioxid and 80 per cent. oxygen. The time recorded is in one-fifths of a second. The

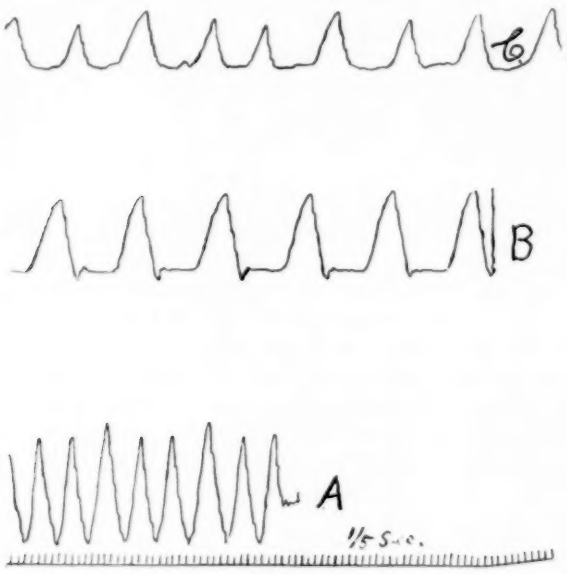

Figure 2

lower line A, Figure 2, records the respiratory excursion while the dog was rebreathing this high percentage of carbon dioxid. The largest tidal air recorded was 484 c.c. Both phrenic nerves were then sectioned in the lower cervical region and the respiration recorded on line B. The largest tidal air recorded was 330 c.c.

The linea alba was then incised up to the diaphragm and all the attachments of the abdominal muscles to the costal borders and last rib were severed. Tracing C was then made and the largest tidal air was 220 c.c.

CONFORMATION OF THE THORAX AND MANNER OF COSTAL EXCURSION

Before entering on a discussion of muscular function, the next problem to consider is the conformation and excursion of the thoracic cage. The bony cage of the thorax consists of two parts, whose mechanisms of respiratory excursion differ in several details. The

upper portion, or cuirass, consists of the sternum and upper five ribs, which unite transverely with the sternum at nearly right angles. In inspiration the anterior transverse portions of the second to the fifth ribs (inclusive) are rotated in a vertical plane which intersects the rib at its midclavicular line and the articulation between the head of the rib and the transverse process of the vertebrae. The lateral parts of these ribs rotate in a vertical plane which intersects the rib in its midaxillary line and the middle of the median plane of the thorax. Both of these radii of rotation for these four ribs increase in length from above downward as their arches increase in size.

In the Hamberger model, which supposedly represents the elevation of the ribs, the radii of rotation for rib segments are wrongly employed to represent the ribs, and, therefore, show a widening of the distance

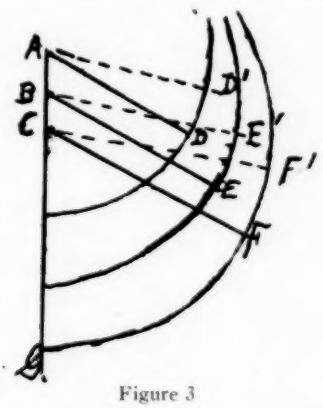

Figure 3

between these supposed structures as they move upward in parallel relation. The widening is true for the radii of rotation of rib segments but not for the intercostal spaces, which should be measured by the distance between the ends of the radii. This will be seen in Figure 3.

In the above diagram let A-G be the vertebral column and A-D, B-E and C-F the radii of rotation of the anterior parts of three ribs. As the radii move upward or in a cephalad direction, retaining the parallel relation so that they are brought into the positions of A-D', B-E' and C-F', the distances between the parallel radii increase but the distances between the ends of the radii diminish; and it is the distance between the ends of the radii which should represent the breadth of an intercostal space. An apparatus was designed to illustrate this point (Fig. 4).

In Figure 4, A, the large perpendicular piece represents the side of the vertebrae. The three parallel structures at bent angles with the

vertebrae represent the radii on which segments of the arches of the upper ribs rotate. The three transverse pieces attached to the ends of the radii represent segments of the arches of the ribs, and the three rubber bands which connect the segments of the ribs represent the intercostal muscles.

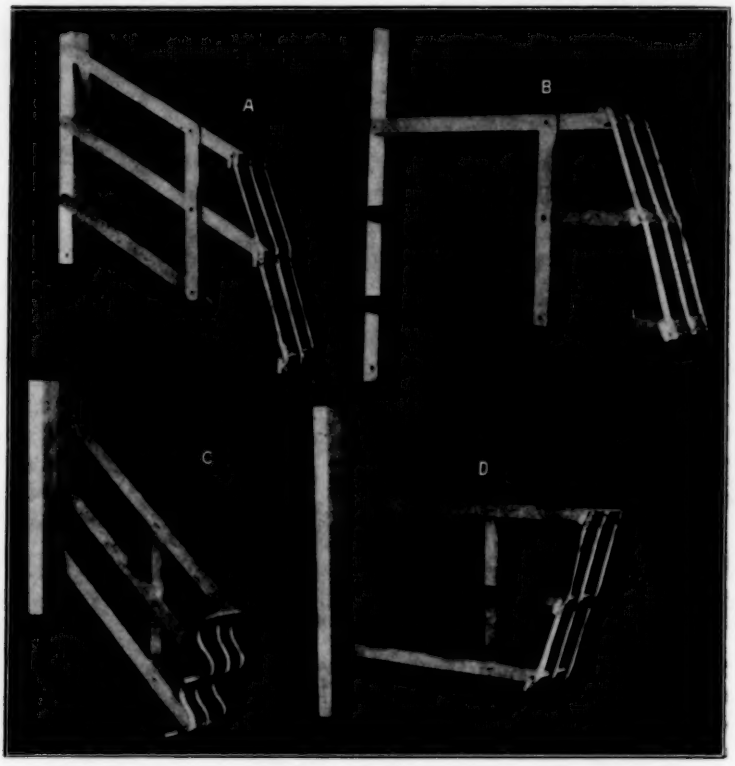

Figure 4

In B, as the three radii are released they rise to a right angle position on the vertebrae. The distances between the radii are enlarged, but the elastic bands which represent the intercostal muscles are shortened.

If the apparatus is turned upside down, we then have an illustration of the ribs at the base of the thorax where the arches of the ribs diminish in size as we descend.

In C, the three arms forming acute angles with the perpendicular median plane of the thorax represent the radii of rotation of the ninth,

tenth and eleventh ribs. When the radii form an acute angle with the perpendicular, the bands representing the intercostal muscles are relaxed, and then if the radii are lifted into the horizontal position, as in D, the intercostal bands become taut. This is just the opposite of the conditions which obtain in the upper thorax, where elevation of pairs of ribs in parallel relation narrows the intercostal spaces throughout their entire extent. In the middle of the thorax, where the succeeding lower rib has the same sized arch, or in the lower thorax, where the succeeding lower rib has a lesser arch, elevation of ribs in pairs would widen the intercostal spaces but for provisions in the structures of the anterior extremities of the last seven ribs. From the sixth to the tenth rib, inclusive, the angulation of the cartilaginous parts of the ribs with their bony parts permits an enlargement of the costochondral angle as the rib is elevated, and thus the entire arch of the rib is enlarged as it is drawn upward and outward by the intercostal muscles. The straightening of the costochondral angle thus permits all that part of the rib which is lateral to the chondral portion to be rotated outward in a horizontal plane on a vertebral axis. The capacity for outward rotation on a vertebral axis increases from the sixth to the twelfth ribs, inclusive, and is particularly ample in the floating ribs. If these last seven ribs move upward in response to activation of the intercostal muscles attached to their upper borders, they must swing laterad, and thus, by increasing the length of the radii of cephalad rotation of their arches, the intercostal spaces retain a constant breadth. This introduction of an additional axis of rotation for the lower seven ribs compensates for the widening of their intercostal spaces that of necessity would result if the radii of rotation of their arches were not enlarged as they are elevated during inspiration.

It is an absurdity to suppose that direct action of the intercostal muscles in any phase of quiet respiration could possibly widen the spaces between ribs. The mechanism just described shows how elevation of the ribs increases the circumference of the thorax at every level without stretching the parietal pleura, and maintains a constant breadth of the intercostal spaces. In fact, the function of the intercostal muscles during inspiration is to elevate the ribs without widening the intercostal spaces. The visceral pleura glides over the parietal pleura only in pulmonary excursion between the position of apnea (i. e., the end of passive expiration) and that of maximum inspiration, and within this range of thoracic excursion the parietal pleura is maintained as a smooth, taut membrane—a condition that is very essential for the smooth functioning of lung extension. From the position of apnea to that of forced expiration, when the ribs are all pulled downward and the lower seven are rotated mediad on their vertebral axes by the action of all the intercostals and the abdominal

muscles, so that the surface of the parietal pleura may present a slightly corrugated surface; but within this range of thoracic excursion there is no gliding between the visceral and parietal pleurae.

This exposition of costal excursion clearly shows how the intercostal spaces, from the second to the fifth, inclusive, may either retain their breadth or be slightly narrowed in the process of increasing the circumference of that part of the thorax which has the rigidity of a cuirass; and it also shows how, if the ribs be permitted to move cephalad during inspiration, the lower intercostal spaces, from the sixth to the eleventh, inclusive, must retain their width unchanged by an outward rotation of the ribs on a vertebral axis. If this outward movement of the lower ribs is not allowed, then the lower part of the thorax is rib-bound and loses its contribution to pulmonary excursion in inspiration.

It thus become apparent how flattening of the subcardial and lateral portions of the diaphragm will lessen the vital capacity of the lungs not only because some phrenic excursion is lost but also because flattening of any part of the diaphragm lessens the outward rotation of the costal ends to which it is attached. Depression of the diaphragm renders a patient, so to speak, both phrenic bound and costal bound in the lower thorax. In cardiac disease, where the enlarged heart flattens the subcardial diaphragm and causes inspiratory narrowing of the subcostal angle, we can see how the loss of outward rotation of the involved ribs will contribute to a loss in vital capacity of the lungs. So that cardiac decompensation contributes to lessening of lung capacity not only by lung rigidity from stasis in the pulmonary circulation, but also by costal rigidity due to a loss of outward rotation in the sixth to the ninth ribs, inclusive.

To show the absurdity of the supposed widening of the intercostal spaces on inspiration, one needs only to stretch a tape from the top of the second rib in the midclavicular line to the eleventh rib in the midaxillary line, and it is then seen that from the end of a normal expiration, or the position of apnea, to a maximum inspiration, the distance between these two points remains unchanged. If the tape is stretched from the middle of the clavicle to any point on the lower ribs, the distance between the two points is found to be lessened during quiet inspiration. In other words, all excepting the first rib move cephalad during a moderate inspiration. In a forced inspiration the scaleni elevate the first rib and with it the clavicle.

Excepting the first interspace, every part of all the intercostal spaces retains an unchanged breadth during tranquil inspiration, excepting those parts which lie between the costal cartilages as they form an angle with the course of their respective rib and turn in a cephalad direction to join the sternum. These interchondral spaces

are decidedly widened during inspiration, as can be clearly seen in the dog when the intercostal spaces are uncovered. However, in this area of interchondral spaces, a considerable volume of muscle intervenes between the spaces and the parietal pleura, viz., the triangularis sterni and the transverse abdominal muscles; so the alternate widening and narrowing of these spaces with respiratory movements do not modify the contour of that part of the parietal pleura that lies underneath.

This exposition of costal excursion is confirmed by a dog experiment which was designed to produce an exaggeration of the normal excursion of the ribs.

EXPERIMENT 4. — Under morphin, ¼ grain, and ether anesthesia, both phrenic nerves were severed in the lower cervical region, and all the attachments of the abdominal muscles were cut away from the costal margins, and the ribs exposed by skinning one side of the thorax. By this means all restraint to costal excursion by the diaphragm and abdominal muscles was

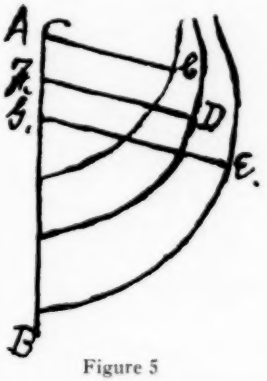

Figure 5

abolished. The dog was then made to rebreathe through a tracheal cannula connected with a Benedict reservoir that contained 25 per cent. carbon dioxid and 75 per cent. oxygen. The tube connecting the trachea with the reservoir was narrowed by means of a screw clamp so that inspiration and expiration were both much prolonged. It was thus possible to make a satisfactory inspection of the costal movements.

The second rib touched the first rib at the height of inspiration, and the second interspace was narrowed but not so much as the first. The narrowing of the interspaces during inspiration grew progressively less to the seventh, which retained an unchanged breadth during the entire respiratory cycle; but from the seventh space down to the twelfth, inclusive, there was a perceptible widening of the interspaces during inspiration and narrowing at the end of the forced expiratory effort. These observations were made on the intercostal spaces in a line drawn from the midclavicular line on the second rib to the midaxillary line on the thirteenth rib. It was clearly perceived that the interspaces in the upper half of the thorax, or cuirass, were narrowed in inspiration and widened in expiration, but in the lower half the interspaces were widened during inspiration and narrowed with expiration.

This strongly indicates that the intercostal muscles are concerned wholly with rotation of the ribs in laterad, cephalad and caudad directions, and have nothing to do with the breadth of the intercostal spaces. The varying breadth of the intercostal spaces is a mere incident in the process of enlarging the circumference of the thorax in all its levels during inspiration, and constricting the thorax circumferentially during expiratory efforts.

Figures 5 and 6 illustrate the rotations of the intercostal spaces in forced expiration.

In Figure 5 A-B represents a line drawn through the costovertebral articulation of three upper ribs. C, D and E are points on the first, second and third ribs in the mid-clavicular line. A-C, F-D, and G-E are the radii of

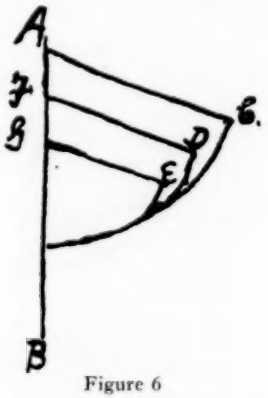

Figure 6

rotation of the points on the ribs. The distances between the arcs of rotation of these radii are seen to broaden as the arcs are drawn downward, which of course means that the intercostal spaces are slightly broadened in this part of the thorax as the ribs are pulled downward from the position of apnea to that of forced expiration. As we descend to the lower position of the thorax, there is a distinct narrowing of the intercostal spaces with forced expiration. This mechanism is described in Figure 6.

In Figure 6 let the line A-B represent a line on the middle of the vertical plane of the thorax, and C, D and E points on the ninth, tenth and eleventh ribs in the midaxillary line. A-C, F-D, and G-E are the radii of rotation of the points on the arches of these ribs, which diminish in size from above downward. As these rius are drawn mediad and caudad, the ends of the radii of rotation of neighboring costal segments, as shown by the arcs of excursion of the points C, D and E, will be approximated.

Thus, in thoracic excursion from the postion of apnea to that of maximum expiratory compression, the upper part, or cuirass, and the lower or bellows part are both diminished in circumference, but in this process the upper intercostal spaces are slightly broadened and the lower intercostal spaces are narrowed.

COMPRESSION OF THE LUNGS BY INTERCOSTAL MUSCLES

As shown thus far by this study, the active part that the intercostal muscles may perform in compressing the lungs indicated the need of proving that the intercostals without the aid of the abdominal muscles can raise the pressure in the pleural cavity. The loss of one half the power of lung compression in our patient with paralyzed intercostals and intact abdominal muscles demanded proof that the intercostals without the aid of the abdominal muscles can compress the lungs.

Five animals were employed for this purpose. In four of them the abdominal muscles were eliminated by cutting all their attachments to the thoracic cage, and in one dog the dorsal cord was sectioned at the level of the fifth dorsal vertebra. The Meltzer pleural cannula and a tambour were used in each experiment to record the intrapleural pressure. The pleural cavity was injected with 100 c.c. of air to insure against occlusion of the intrapleural opening of the cannula, and after each tracing the contained air was aspirated by a graduated syringe to make sure there had been no leakage of air into the pleural cavity. The dog was made to rebreathe an atmosphere of 80 per cent. oxygen and 20 per cent. carbon dioxid against stenosis equal in inspiration and expiration and as great as the animal would tolerate—i.e., the maximum resistance against which the dog would continue to breathe.

The rise in pleural pressure in expiration was always very moderate, only about one-quarter as great as the minus pressure obtained during inspiration. There was some doubt as to whether the moderate positive pressure attained in expiration was due to action of the intercostals or merely to pressure of the expanded thoracic cage passively resting on the lungs after they had been distended by torsion of the thorax and descent of the diaphragm during inspiration.

In several experiments only ¼ grain morphin was given before ether anesthesia was employed, and the animal was permitted to come sufficiently out of the ether anesthesia so that the conjunctival reflex returned. The idea was then conceived that the preliminary dose of morphin or the ether was responsible for the high threshold for active expiration, and therefore nitrous oxid anesthesia was employed without any preliminary dose of morphin. The results obtained by this method were very satisfactory.

EXPERIMENT 5.—The dog with which the following tracings were made was a vigorous 2-year old terrier, weighing 12 kilos. The nitrous oxid anesthesia was begun by giving the anesthetic with a muzzle over the dog's nose while a tracheotomy was done, a tracheal cannula placed in position, and a Meltzer cannula inserted in the fourth intercostal space of the right side. An apparatus like that used in the surgical department of Lakeside Hospital was employed, and the anesthesia was administered by one of the anesthetists of the surgical service.

The original plan was to cut away all attachments of the abdominal muscles to the thoracic cage while the animal was under the anesthetic, and then with suspension of the nitrous oxid it was planned to give the dog a dose of apomorphin with the idea that during the vomiting effort that would follow, the action of the intercostals might produce a strong positive pressure in the pleural cavity. Quite beyond all expectation, while the dog's abdomen was still intact and without the introduction of any further resistance to expiration than was provided by the apparatus as usually employed in surgical work, the intrapleural tracing revealed a very strong positive pressure during expiration. After the tracing was finished, the pleural cavity was exhausted of air and only 100 c.c. could be withdrawn, the exact amount that was injected before the tracing was begun. It is, therefore, quite certain that pneumothorax was not a factor in the intrapleural pressure obtained.

In Figure 7, tracing A was made of the intrapleural pressure when the abdominal muscles were intact and there was no resistance offered to the entrance and exit of air beyond what the apparatus supplied. The time tracing is in seconds, and the horizontal line traces barometric pressure. The inspiratory or downward stroke is straight and the upward or expiratory stroke is equally so. As the tracing shows, each expiration was active and was attended by vigorous contraction of the abdominal walls. There was a free exchange of air between the lungs and the elastic bag that contained the mixture of nitrous oxid and oxygen. The intrapleural pressure, as determined by calibration of the tambour directly after the experiment, ranged between 80 and 130 mm. of water above barometric pressure and between 60 and 80 mm. of water below. The extent of intrapleural pressure does not indicate the volume of tidal air, because the intrapulmonic pressure was above the barometric. However, the excursions of the walls of the rubber bag showed the animal was freely exchanging air, and at the conclusion of the tracing, when the trachea was disconnected from the nitrous oxid apparatus, there was no hyperpnea.

This was a far better exhibition of active expiration under anesthesia than I had ever succeeded in procuring. It was therefore decided to cut away the attachments of the abdominal muscles from the thoracic cage and then see how the intrapulmonic pressure would behave with expiration under the influence of nitrous oxid.

Apomorphin was not given when the abdominal muscles had been cut, and the anesthetic was continued as before. Both inspiration and expiration were apparently conducted with much vigor. The whole surface of the diaphragm was plainly in view and could be seen to contract vigorously with inspiration. During expiration the under surface of the diaphragm pouched slightly caudad, and could be felt by the palpating hand to be under rather high pressure during the entire expiratory phase.

Tracing B, Figure 7, was then made of the intrapleural pressure. When this tracing was made, the only muscles that could possibly contribute to overcoming the intrapulmonic pressure were the intercostal muscles, the triangularis sterni, and some of the serratus posticus inferior. It seems certain that the intercostals must have been the dominant agent in compressing the lungs. The excursion of the thoracic cage was vigorous, and the costal borders were strongly moved lateral during inspiration.

At the right of the middle of the tracing the intrapulmonic pressure was nearly sufficient to distend the lungs, as shown by the fact that the intrapleural pressure during inspiration descended very little below the barometric line. That the dog was freely exchanging air was indicated by the thoracic excursion and the movements of the bag containing the anesthetic. At A the valve in the lateral opening of the tube connecting the tracheal cannula with the rubber bag was opened more freely to reduce the intrapulmonic

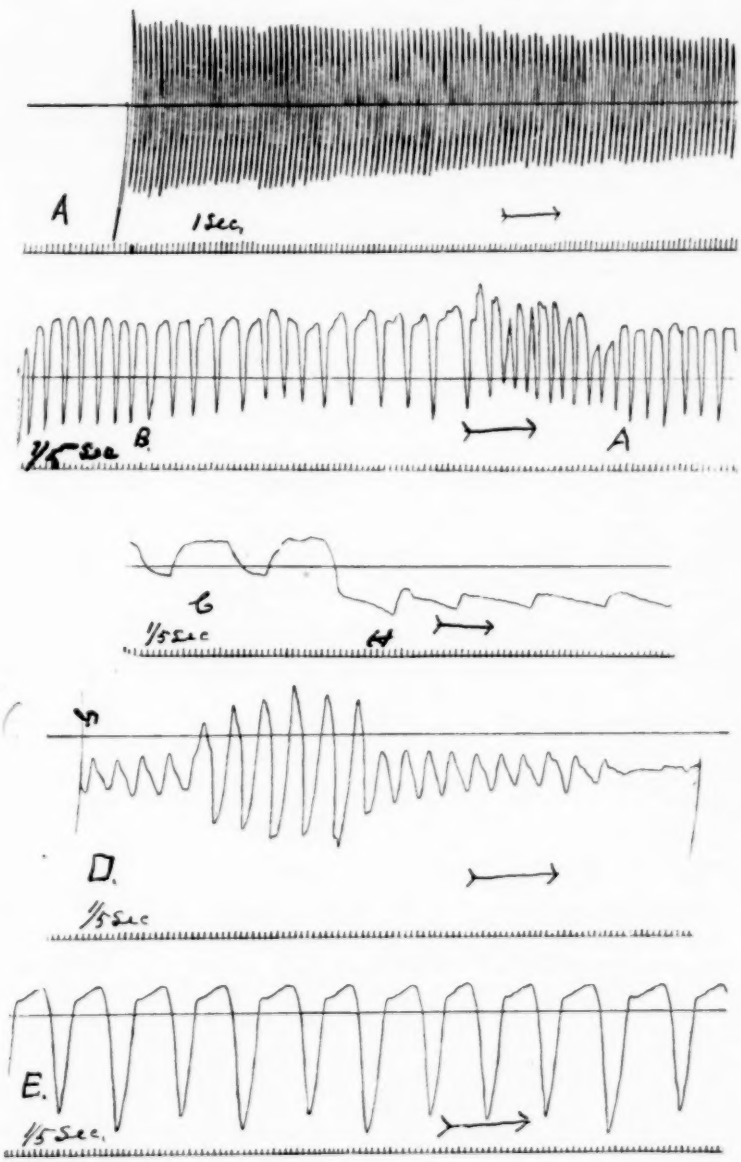

Figure 7

pressure. Immediately the inspiratory excursions of intrapleural pressure below the barometric line increased and the expiratory excursions above diminished.

The time markings in this tracing are in fifths of a second. The horizontal line traces barometric pressure. The pressure above the barometric line ranged between 120 and 60 mm. of water, and that below between 60 and 10 mm. of water, the pressure above the line being greatest when the pressure below was least.

In Figure 7, tracing C is from the last part of the tracing shown in B. The ten respiratory cycles with the two that preceded H were all alike, having a duration of eight-fifths second for inspiration and twelve-fifths second for expiration. The intrapleural pressure in inspiration descended only 15 mm. of water below barometric pressure, but during expiration it ascended 40 mm. of water above. Then as the tracheal cannula was disconnected from the nitrous oxid apparatus at H, the character of the respiration changed. The intrapleural pressure remained below the barometric line and during inspiration descended to 50 mm. of water.

The air was then aspirated from the pleural cavity and 100 c.c. were obtained, the exact amount injected before the tracing in B and C was begun. That the dog was freely exchanging air during this period is shown by the want of hyperpnea as the tracheal cannula was disconnected from the apparatus.

In Figure 7, line D is the intrapleural tracing while the dog was freely breathing room air through the tracheal cannula. In the six respiratory cycles in which the expiratory pressure goes above the barometric line, the dog's thorax was strongly compressed laterally during expiration between my two hands. During this compression, the under surface of the diaphragm was depressed. The moderate rise of intrapleural pressure during this procedure gives some idea of the vigor with which expiration was accomplished in the periods when the preceding tracings were made.

The dog was then given ether, and a large amount of air admitted to the pleural cavity through the Meltzer cannula. The pneumothorax was of such degree that during expiration the entire under surface of the diaphragm projected as a convex dome below the costal borders. During this period tracing E, Figure 7, was made. The time was in one-fifths of a second, expiration occupying eight-fifths second and inspiration three-fifths second. During expiration the intrapleural pressure rose only as high as 40 mm. of water above the barometric line, but during the brief inspiration the pressure descended to 180 mm. of water below. I have in former experiments frequently traced the intrapleural pressure of dogs with severe pneumothorax when morphin and chloretone or morphin and ether were used for anesthesia, and many of the tracings were like this one.

The mechanisms involved in breathing against a positive intrapulmonic pressure seemed to require further consideration. For this purpose another experiment was made with nitrous oxid anesthesia, in which the same apparatus was used as in the preceding one.

EXPERIMENT 6.—A T-tube was put in the tube connecting with the tracheal cannula, and by means of its lateral branch the intrapulmonic pressure could be traced by a tambour at the same time the intrapleural pressure was recorded by a tambour connected with a Meltzer cannula in the fourth right intercostal space in the midclavicular line. The writing styles of the two tambours were perfectly aligned, so that the intrapulmonic and intrapleural pressures could be compared at any phase of a respiratory cycle.

The dog was a terrier weighing 9.5 kilos. Nitrous oxid and a little ether were used while the preliminary tracheotomy was performed and the tracheal

cannula fixed in position. Only nitrous oxid and oxygen were subsequently used. The tracing was made while all the muscles involved in respiration were intact.

In Figure 8 the upper line is the tracheal, and the lower line the intrapleural tracing. The horizontal line in each traces the line of barometric pressure. In both, the upstroke traces expiration and the down stroke inspiration. The time marker is in seconds in the slow drum, and in one-fifth second in the fast drum. During the time the tracing was made the abdominal muscles were firmly contracted during expiration, and the respiratory exchange was free between the lungs and the rubber bag containing the anesthetic.

The tambours were calibrated against a water manometer directly after the experiment. At the end of expiration pressure in the pleural cavity equaled 180 mm. of water and in the trachea 160 mm. During inspiration the intrapleural pressure attained between 100 and 55 mm. of water below the barometric line, and in the trachea at the end of inspiration the pressure was never less than 40 mm. of water above the barometric line.

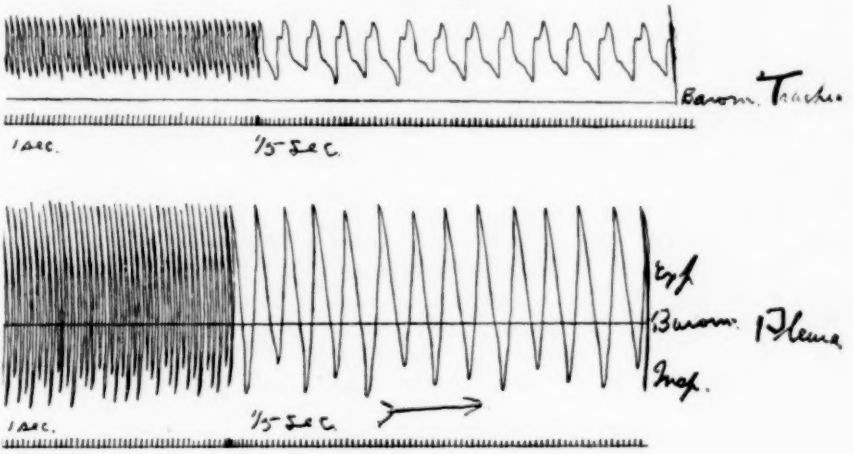

Figure 8

The question might be raised as to how much the expiratory recoil of the distorted thorax can be responsible for the rise in pressure in the pleural cavity. For it may be thought that the recoil of the thorax against the lung distended by intrapulmonic pressure may be responsible for the rise. If we consider the physical conditions at the end of expiration, it is apparent they were as follows: In the pleural cavity there was a pressure of 180 mm. produced by the expiratory muscles with the supposed aid from thoracic recoil, and in addition to these factors there was the elastic contraction of the lung, which at the end of expiration balanced a column of water 40 mm. high—in all representing an expulsion pressure of 220 mm. These forces were pitted against an intrapulmonic pressure at the end of expiration equal to 160 mm. of water. But if we consider for a moment, we shall see that

at the end of an expiratory phase there can be no available force from recoil of the thorax. Instead of recoil in an expiratory direction, there is some potential recoil in an inspiratory direction, as can be shown when air is admitted to the pleural cavity so that barometric pressure is produced. Under such conditions the thorax increases in volume. It is thus apparent that the 180 mm. of pressure registered in the pleural cavity at the end of expiration was due wholly to action of the expiratory muscles. This experiment confirms the interpretation of the intercostal source for the intrapleural pressure shown in the preceding tracings of Figure 7. It also furnishes another bit of evidence to show that inspiratory and expiratory forces are equally provided for all the boundaries of the lungs—a conception that is very important for the interpretation of clinical signs pertaining to respiratory excursions of the thorax.

All of the foregoing observations are in direct conflict with two points of view which seem to be generally accepted by physiologists. The prevailing physiologic belief is that widening and narrowing of the intercostal spaces are purposes for employment of the intercostal muscles. It is very obvious from the foregoing observations that if all of the external intercostal muscles are synchronously activated during inspiration, their purpose cannot be to widen all the intercostal spaces, for if the breadth of the intercostal spaces is modified at all during inspiratory excursion, the upper interspaces are narrowed and the lower widened, and during expiration the reverse of this is true. So that obviously, if all the internal intercostal muscles are synchronously activated during expiration, they cannot serve the same purpose in all the intercostal spaces if the modification of the breadth of the spaces is the purpose of their contraction. The chief function assigned to the intercostal muscles by physiologists is the fixation of the sides of the thorax to furnish rigidity to the intercostal spaces. But it was observed in our patient who had paralysis of all the intercostal muscles that he did not in any degree suffer from a want of resistance to atmospheric pressure in the intercostal spaces. The parietal pleura amply serves such a purpose. He did suffer distinctly from an impairment of his vital capacity, but the greatest disability he suffered was the great loss of the intercostal muscles for forcibly constricting and expanding the thorax. If this man were to suffer an attack of bronchiolar hypertonus sufficiently severe to demand an active expiratory effort as well as a vigorous inspiratory effort, he would probably succumb to suffocation. It does not seem possible that he would be able to employ sufficient effort in inspiration and expiration to escape such a fate in view of the violent effort at expansion and constriction of the thorax which is employed by persons with normal musculature in attacks of bronchiolar hypertonus.

MOVEMENTS OF THE FIRST RIB AND STERNUM

This patient with paralysis of the intercostal muscles had an excursion of the sternum and first pair of ribs that is of interest in relation to the normal function of the scaleni and first pair of intercostal muscles. By the use of the scaleni alone, he could increase the circumference of the thorax three-fourths of an inch at the third and sixth intercostal spaces. The increase in circumference below the subcostal angle was due wholly to protrusion of the upper abdomen from descent of the diaphragm. Because of the anchorage of the manubrium and first pair of ribs by the scaleni, these structures are stationary in a normal person with quiet breathing. They move cephalad only in forced inspiration, but in the patient with paralyzed intercostal muscles the manubrium and first rib moved cephalad during quiet breathing, because the normal opposition of the first intercostal muscles to the scaleni was wanting. The balance between the pull of the scaleni and the first intercostal muscles indicates an isometric contraction of the scaleni. The scaleni are activated during quiet inspiration, as indicated by the cephalad movement of the manubrium and first rib in quiet respiration in the case of our patient with paralysis of the intercostal muscles, but in a normal person the origin and insertion of the scaleni are not approximated during activation in tranquil breathing, but without their activation the manubrium and ribs to which they are attached are moved in an expiratory direction during the inspiratory phase. When the scaleni are paralyzed, the manubrium and first, second and third ribs move caudad on inspiration. The fourth rib is stationary, but below that there is an exaggerated movement in a normal direction. A discussion of this subject will be found in a previous publication.[1]

Studies of the movements of the first rib and all those below show that in quiet breathing the first rib is not elevated; below the second rib there is no demonstrable variation in the breadth of the intercostal spaces; and isometric contraction prevails in the scaleni and all the external intercostals. Shortening of any of these muscles is not an essential to their employment. They may all be vigorously employed without being shortened, and whether they are shortened or not will depend on the fixation of the muscle at one point of insertion. As mentioned, in the patient who had paralysis of his intercostal muscles the first rib and manubrium moved cephalad during tranquil respiration because of want of fixation of the first rib by normally acting intercostal muscles, and in the child who had paralysis of the scaleni there was distinct narrowing of the upper three intercostal

1. Hoover, C. F.: Diagnostic Signs from the Scaleni, Intercostal Muscles and the Diaphragm in Lung Ventilation, Arch. Int. Med. **20**:701 (Nov.) 1917.

spaces, attended with caudad movement of the upper three ribs when their intercostal muscles were activated during inspiration. This caudad or expiratory movement during the inspiratory phase was due to want of fixation of the upper three ribs by normally acting scaleni.

Because of the normal anchorage of the manubrium and first pair of ribs by the scaleni during inspiration, the distance between two points—namely, on the second rib in the midclavicular and on the tenth in the midaxillary line—is unchanged in thoracic excursion within the range from apnea to maximum inspiration, but normally in tranquil breathing the distance between points on the middle of the clavicle and on the tenth rib in the axillary line is diminished. In our patient, on the left side where all the intercostals were paralyzed, the distance between the clavicle and the tenth rib and between the second and tenth ribs remained the same during quiet and forced breathing.

Under normal conditions the sternum in inspiration is rotated anteriorly on a transverse axis located at the upper border of the manubrium. The ventral elevation of the anterior parts of the second to the fifth ribs, inclusive, carries forward those parts of the sternum to which these ribs are attached, but in our patient the lower end of the sternum was retracted vertebrad with inspiration, because, as the costal borders were drawn toward the median line by inspiratory traction of the diaphragm, the normally acting subcardial diaphragm drew the sternum vertebrad. In inspiration the lower end of the sternum is also retracted when the subcardial diaphragm is flattened sufficiently to give it the mastery over the intercostals. This occurs in enlargements of the heart or the pericardial sac.

FUNCTIONS OF THE INTERCOSTAL MUSCLES

In the beginning of this discussion, a few brief references were made to the history of the study of costal movements and the functions of the intercostal muscles, and the statement was then made that Martin and Hartwell, in 1879, published the only piece of work that has thus far given any experimental support to the theory that the external intercostals had purely inspiratory and the internal purely expiratory functions. The sources of the difficulty lie in the facts that physiologists cramped their minds into believing that all the intercostal spaces were widened during inspiration as an essential part of lung enlargement; but when the intercostal spaces are studied on an animal with an intact thorax, it is found that the spaces remain unchanged in a normal respiratory cycle, and in exaggerated inspiration the upper spaces narrow and the lower widen. If the muscles connecting any two ribs are activated by an electric current, the ribs are approximated when both external and internal muscles or only one of them is intact.

Under the discussion of costal movements it was shown how under

normal conditions the intercostal spaces must all, with the exception of the first, retain a constant breadth in a respiratory excursion ranging between the position of apnea and that of maximum inspiration. But it will also be remembered that, when the scaleni are paralyzed, the first three intercostal spaces are much narrowed during inspiration, the first three ribs move in a caudad direction and the fourth rib remains stationary, while the remaining eight ribs move in a normal direction.

In this relation there is another observation of importance that was made on the patient who had all but the lower four right intercostal muscles paralyzed. When the patient was seated and the examiner, standing behind him, placed a palpating finger of each hand in the tenth intercostal space of either side in the posterior axillary lines, there was a very perceptible difference between the intercostal spaces of the two sides if the patient made a maximum inspiratory effort. On the right side the tenth and eleventh ribs moved in a normal manner and the breadth of the intercostal space was unchanged, but on the left side, where all the intercostals were paralyzed, there was a perceptible widening of the intercostal space and the intercostal structures were retracted and drawn taut as the strong inspiratory effort was made. The patient's scaleni were normal; so when by their maximal activation the upper thorax was drawn upward, the traction applied to the upper two ribs by the scaleni served to elongate the thoracic wall of the entire left side by a very slight but perceptible widening of the intercostal spaces.

When in a seated position this patient made a strong inspiratory effort, the circumference of his thorax at the third and sixth interspaces increased three-fourths of an inch, although all the intercostal muscles of both sides in these parts were paralyzed. This increase in circumference was due entirely to the scaleni, which by their attachments to the first and second ribs not only drew these ribs upward but exerted a cephalad traction on all the ribs below by means of the connections through the parietal pleura, which is capable of very slight extensibility. The increase in circumference of the upper three quarters of the thorax was accomplished by the action of the scaleni only, and as already shown it would be impossible to elevate the ribs in their parallel relation without narrowing the intercostal spaces or retaining a constant breadth between them. The very limited extensibility of the parietal pleura allows only a slightly perceptible broadening of the spaces. It will be remembered that in this patient all the intercostal muscles of the left side and all but the lower four on the right were paralyzed. When a tape, fixed on the third rib in the left midclavicular line, was drawn taut to the tenth rib in the left midaxillary line, the distance between these two points was very slightly increased

by a maximum inspiration. When during a forced inspiration the upper end of the tape was fixed on the middle of the clavicle, the distance between the clavicle and the point on the tenth rib showed about the same increase. On the right side, where the lower four intercostals only were active, when symmetrical measurements were made in the same manner, the distance from the third to the tenth rib in inspiration was found to be shortened by a distance equal to the breadth of one interspace, and the distance from the clavicle to the tenth rib was diminished as in normal persons.

When the lower intercostal spaces of the right side were examined, the eighth intercostal space was found to be narrower than that immediately above and below. This was due to paralysis of the seventh intercostal muscle and the downward traction of the eighth rib by the intact muscles of the eighth interspace. During inspiration the ninth rib moved with vigor in a normal direction, but its excursion was perceptibly less than that of the tenth, eleventh and twelfth. After a little practice in palpating ribs, the examiner will readily distinguish between the movement of a rib that passively yields to the traction of its intercostal attachments and a movement that is conferred on it by action of its attached intercostal muscle.

The effect of paralysis of an external intercostal muscle on the breadth of its interspace is shown by a very simple experiment. The ribs and intercostal muscles are exposed in the middle part of one side of a dog's thorax and the external intercostal muscle of the eighth interspace severed in its middle for its entire extent. During tranquil respiration the eighth space is then seen to widen during inspiration by an upward movement of the eighth and a lesser downward movement of the ninth rib.

It is quite clear, then, that action of the intercostal muscles either narrows or preserves the upper intercostal spaces unchanged, and the only interspaces that are widened by inspiration are those spaces between the lower chondral cartilages as they form angles with their respective ribs to pass cephalad toward their junction with the sternum. It now remains to be shown how the external and internal intercostal muscles are brought into requisition by different kinds of respiratory movements.

A normal person can aspirate a column of mercury 90 mm., and blow a column 100 mm. high. Aspiration is done by the diaphragm, intercostals and scaleni; compression of the lungs, by the abdominal muscles and the intercostals. When the intercostals were paralyzed, a man who normally should be able to blow a column of mercury 100 mm. was able with powerful abdominal muscles to blow a column only 50 mm. high, and aspirate by his diaphragm and scaleni a column only 46 mm. These results proved that in a normal person the share of the

intercostal muscles in forced inspiration is equal to that in forced expiration; and, therefore, in the act of compression, all the intercostal muscles are employed both in depressing and in elevating the ribs if the maximum inspiratory and maximum expiratory efforts are made. So if approximation of the ribs by intercostal action is to be observed, it is advisable to study the movements of an adjoining pair of ribs when they are cut away from their costal attachments above and below and freely respond to activation of the muscles connecting them. By severing the connecting external muscle in one instance and the internal in another, we are able to see under what respiratory conditions both the external and internal muscles are brought into action. However, if the threshold of employment for the internal intercostals only is to be studied, the thorax can be left intact and the external intercostals severed for their entire extent in two neighboring intercostal spaces. The dog is then made to rebreath an atmosphere with a high carbon dioxid content to induce hyperpnea, and by applying compression to the tube connecting the bag with the tracheal cannula, the behavior of these muscles can be brought out when great effort in expansion and compression of the lungs is employed.

The results obtained by animal experiment in the study of intercostal muscle employment vary with the anesthetic and the depth of anesthesia, and also with the stage of exhaustion of the respiratory innervation. The intercostal muscular response also varies with the amount of tidal air demanded by the respiratory need and with the resistance to inspiration and to expiration. To get the best results the respiratory threshold should be raised as little as possible by the use of anesthesia. The less the respiratory threshold is raised the greater is the alertness and vigor in the respiratory efforts that follow when the animal breathes a high concentration of carbon dioxid or is made to work against resistance to the entrance and exit of air.

THRESHOLDS FOR EMPLOYMENT OF THE EXTERNAL AND INTERNAL INTERCOSTALS

Experiments were made to gain information about the thresholds of employment for the two sets of intercostal muscles in inspiration and expiration.

EXPERIMENT 7.—After the ribs and intercostal muscles have been exposed over one side of a dog's thorax, the external intercostal muscle in the eighth interspace is severed in the middle intercostal line from its anterior border to the vertebra. Then, while the animal is tranquilly breathing room air, the space between the two ribs, united only by the internal intercostal muscle, widens with inspiration, while the spaces above and below remain constant. However, there is thus far no evidence of activation of the exposed internal intercostal muscles. The tracheal cannula is then connected with a bag containing 75 per cent. oxygen and 25 per cent. carbon dioxid. With the ensuing hyperpnea the dog is compelled to speed up his respiratory and expiratory

phases, and the tidal air is greatly increased, so that the expiratory excursion of the thorax exceeds that of the position of apnea. The exposed internal intercostal muscle is then seen to contract vigorously during expiration as the thorax is circumferentially constricted. But thus far there is no evidence of activation of the internal intercostal muscle during inspiration. Apparently the external intercostal muscles are still adequate to move the ribs into their position of maximum inspiration so long as there is no resistance to the entrance of air, but when the tube connecting the bag and the dog's tracheal cannula is narrowed so that a great inspiratory effort is demanded in the presence of hyperpnea, the exposed internal intercostal muscle is brought into action to aid the inspiratory effort. With the intact thorax this action cannot be shown by any other sign than that the two ribs which are connected by only their internal intercostal muscle are no longer separated during the inspiratory effort as they were in tranquil inspiration.

This indicates that the threshold for expiratory employment of the internal intercostal muscle is lower than that for its inspiratory employment. We must consider too that, although the internal muscle was brought into service with expiration before the tube connecting the trachea and bag was narrowed, the abdominal muscles had not yet been actively contracted during expiration, and thus far it has not been proved that the external intercostal muscles are ever employed in expiration.

To investigate the question of the expiratory use of external intercostals, another dog experiment was conducted in the following manner:

EXPERIMENT 8.—After a preliminary dose of ¼ grain morphin, under ether anesthesia the ribs and intercostals of the lower right thorax were exposed. The sixth and eighth intercostal spaces were cut through for their entire extent and artificial respiration employed. The seventh and eighth ribs were then cut at their costochondral junctions and the internal intercostal muscle was severed through its midline for its entire extent, so that the two ribs were united by the external intercostal only. The two remaining parts of the ribs were held in their normal position with the connecting external intercostal muscle slightly taut. Artificial respiration was then suspended, and, as active respiratory movements by the dog were begun in response to suffocation, there was at first no evidence of expiratory activation of the isolated external intercostal muscle, but as the vigor of the respiratory efforts was increased and the abdominal muscles were strongly activated in expiration, as shown by the forceful upward displacement of the vault of the diaphragm and firm expiratory contractions of the abdominal muscles, the external intercostal muscle, which alone united the two isolated ribs, contracted very actively and approximated the ribs. When the abdominal muscles were not activated in expiration, the isolated external intercostal did not contract.

This experiment was repeated several times and indicates a synergic employment of the abdominal muscles and external intercostals in a forced expiratory effort.

Experiment 9, when taken alone, would confirm the observations of Martin and Hartwell, and without further observations would confirm the Hamberger theory that the external intercostals have a purely inspiratory and the internals a purely expiratory function.

EXPERIMENT 9.—After the usual preparatory procedures, the sixth and ninth intercostal spaces were cut through their entire extent, and the seventh, eighth and ninth ribs were cut at their costochondral junctions. In the seventh interspace the internal intercostal muscle was severed midway between the ribs for its entire extent, and the same was done for the external intercostal muscle in the eighth interspace. We then had the seventh and eighth ribs united only by the external intercostal, and the eighth and ninth by the internal intercostal. Artificial respiration was suspended and the arches of the seventh and ninth ribs were held by the hands in their normal anatomical position on the vertebrae. Slight traction was employed to keep the remaining intercostal muscles slightly taut. Then in inspiration, as suffocation induced active respiratory movements, the eighth rib was drawn upward by the external intercostal muscle, which alone united it to the rib above, and during expiration the eighth rib was actively drawn toward the ninth rib, to which it was united by the internal intercostal only.

This procedure was repeated many times, until the respiratory function was greatly exhausted, and then the expiratory contraction of the internal intercostal ceased when the inspiratory action of the external intercostal was still quite active. During the experiment, however, at no time in expiration were the abdominal muscles contracted, and, therefore, there was no expiratory action of the external intercostals; and furthermore, we could not excite the internal intercostals to an inspiratory effort by offering any resistance to inspiration, as was done in the first experiment when the animal was breathing 75 per cent. oxygen and 25 per cent. carbon dioxid with a closed thorax and against a strong resistance to the entrance of air into the lungs.

These experiments show that the external intercostals under all respiratory conditions are activated during inspiration, and that in tranquil respiration none of the intercostal muscles are employed in passive expiration. During active expiration the internal intercostals are brought into action when the abdominal muscles are not yet needed, but when active expiration enlists the aid of the abdominal muscles, the external intercostals are synergically activated with them.

With an open thorax the conditions forbid the employment of measures that will exceed the threshold for the inspiratory use of the internal intercostals, but so far as could be determined with a closed thorax, the internal intercostals were brought into service when the animal was made to inspire against a high resistance in the presence of great hyperpnea induced by rebreathing an atmosphere consisting of 75 per cent. oxygen and 25 per cent. carbon dioxid. When we consider, however, that a normal person can by the use of his scaleni, intercostals and diaphragm aspirate a column of mercury 90 mm. high, and that by use of his abdominal muscles and intercostals the air in the lungs can be compressed to balance a column of mercury only 10 mm. higher, there is good inferential evidence to prove that in a forced inspiratory effort both sets of intercostals are employed, for we know that both external and internal intercostal muscles are employed in efforts at

pulmonary compression when the abdominal muscles are for this purpose brought into use. It must also be remembered that the man who had all but the lower right four intercostals paralyzed was able to raise the pressure in his lungs to a height of 50 mm. of mercury by use of his abdominal muscles, and should have raised it to 100 mm. had his intercostal muscles been normal. By use of his scaleni and his diaphragm, he was able to aspirate a column of mercury 46 mm. high. As we know that the loss in power for constricting the thorax was due to paralysis of both external and internal intercostal muscles, there is good reason to believe that the loss of aspirating power was not due to paralysis of his external intercostals alone, as we should have to believe if the internal intercostals are regarded as having a purely expiratory function.

The foregoing clinical and experimental observations show that the muscular boundaries of the lung—viz., the intercostal muscles and diaphragm—with the aid of the scaleni and abdominal muscles, supply a uniformly distributed power and capacity for expansion and compression over the entire lung surface, and also that the power available for expansion is about equal to that for compression. The synergic use of all these muscles provides the lung with a motor organism that is like what the heart would have if it were endowed with equal diastolic and systolic powers.

The power for circumferential compression and expansion of the lung is equal to the available power for longitudinal compression and elongation. It is clearly proved that both external and internal intercostals are employed to obtain the maximum circumferential compression, and the corollary from this demonstration is that both external and internal intercostals are employed to obtain the maximum circumferential expansile force. The maximum expansile capacity can be obtained without the use of the internal intercostals if there is no resistance to the entrance of air, but when the maximum expansile force is required, the internal intercostals are brought into use. Furthermore, these clinical and experimental observations show that the motor agencies for the ribs are directed wholly toward modifying the circumference of the thorax, and that any changes in the breadth of intercostal spaces are merely incidental to intercostal muscular action and not the purpose of it.

INTEGRATION OF THORACIC MUSCLES

The foregoing discussion shows the external and internal muscles to be employed during both inspiration and expiration, but how they can equally serve both is not yet apparent. The intercostals alone cannot be responsible for the smooth and orderly manner in which the purposeful excursions of the ribs are displayed during the entire cycle of forced breathing. Thus far the only demonstrated intrinsic effect

of intercostal action is to narrow all the intercostal spaces. If this action during both inspiration and expiration were not modified by the actions of other muscles, the results during both phases of respiration would be a disorderly and fruitless procedure that would contribute nothing to either expansion or compression of the lungs. Which muscles serve to integrate the intercostal muscles for an inspiratory effort and which convert their action into an integrated expiratory effort, are questions that demand an answer.

The inspiratory excursion of the upper thorax of our patient with intercostal paralysis was a lifeless, passive movement, like the expansion of the thorax of a cadaver when the sternum is pulled cephalad. The expansion below the level of the subcostal angle was due largely to the inspiratory descent of the diaphragm. On the left side, where all the intercostals were paralyzed, all the ribs moved slightly cephalad in response to action of the scaleni which drew the first and second ribs in a cephalad direction, and all the ribs below passively followed as a result from traction on the broad sheet of parietal pleura, which is firmly united to the ribs at all the costal spaces. On the right side, the same kind of movement was apparent as far down as to the ninth rib, but the last four ribs moved in a normal manner because of the anchorage from above that was transmitted along the parietal pleura by the normally acting scaleni.

The want of integration of the upper three intercostal muscles with the inspiratory act is clearly demonstrated when the scaleni are paralyzed. These intercostal muscles are activated with all the others during inspiration, but instead of inspiratory inflation there is deflation of the underlying lungs. This is so pronounced that the consequent rebreathing between the upper and lower lungs demands an exaggerated excursion of the lower to compensate for the defective excursion of the upper thorax. This phenomenon was so pronounced in the child referred to above that it led to calling medical counsel. In this child the manubrium and upper three ribs moved strongly caudad during expiration. The fourth rib was stationary during the whole respiratory cycle, while from the fifth rib downward there was an exaggeration of the normal excursion.

When in the dog the attachments of the scaleni to the upper three ribs were cut, the same costal movement as seen in the child was reproduced, but with the ribs exposed a more satisfactory inspection could be made. The upper three ribs not only moved in an expiratory direction during inspiration, but there was a want of integration in their excursions. They moved in a disorderly manner. The first rib moved caudad and so did the second, but the first intercostal space was narrowed. The second intercostal space was obliterated by the upper border of the third rib, which overrode the lower border of the second.

The third interspace was also narrowed. In this relation one must recall the fact that in orderly forced expiration all these intercostal spaces are widened as the ribs move caudad, and in the inspiration of quiet breathing these upper three spaces are unchanged in width. When the upper end of the manubrium was anchored by grasping it with forceps and holding it in the position it took at the end of expiration, then the upper four ribs moved in their normally integrated manner. It has been shown in Experiments 5 and 6 that, when the diaphragm is paralyzed and all the attachments of the abdominal muscles to the thorax are severed, it is still capable of great inspiratory and expiratory excursions; the tidal air is comparatively large, and the intrinsic muscles of the thorax cause marked compression of the lungs.

In these experiments the iliocostal muscles were cut between the ileum and last rib. The only integrators that under such experimental conditions could order the inspiratory and expiratory effect of the intercostals were the scaleni, the serrati postici, superior and inferior, and the triangularis sterni. As already shown, the function of the scaleni during quiet respiration is essential for the orderly action of the upper three intercostal muscles, although in such breathing the upper border of the manubrium and first rib are stationary. Without the anchorage of the scaleni, by their isometric activation the upper three ribs move in an expiratory direction during the inspiratory phase and the upper parts of the lungs are deflated. To determine if the serratus posticus inferior may not serve the same purpose for the lower thorax during forced expiration that the scaleni serve for the upper, Experiment 10 was performed.

EXPERIMENT 10.—A dog was anesthetized with nitrous oxid and a cannula put in the trachea, through which the anesthetic was afterward continued. The same apparatus was used as described in the preceding experiment. The dog was turned on his right side and the muscles over the lower right side of the thorax exposed. The latissimus dorsi was cut and the erector spinae exposed. Along the course of each of the last four ribs an incision was made down to the surface of the rib, from beneath the lateral border of the erector spinae, well beyond the lateral extensions of the serratus posticus inferior. By this means the function of the latter muscle was eliminated, but the intercostal muscles were preserved. The linea alba was then cut from the diaphragm to the pubis, and a transverse incision on both sides eliminated all the abdominal muscles and the iliocostals in expiration. The triangularis sterni was still intact, but it could not play any part in the expiratory excursion of the last four ribs. The conditions of the two sides of the thorax were the same, with the exception that on the right the serratus posticus inferior was eliminated and on the left it was intact. The last four ribs could be palpated on both sides through the intervening diaphragm, which was relaxed during expiration. By placing alternately the four finger tips of either hand on the inner surfaces of the last four ribs of the right and left sides, a decided difference could be detected in the manner of their expiratory excursions. On the right side, where the serratus posticus inferior was wanting, the last four ribs were approximated during expiration, much in the same manner as the four fingers are drawn together by the interossei. On the left side the last

rib and the three above it were drawn forcibly in an expiratory direction, and the approximation of the ribs during expiration was much less than on the right side. The disordered movement of the lower right ribs in active expiration was analogous to the disorderly movement of the upper ribs during inspiration when the scaleni were eliminated. In the middle and upper parts of the thorax it is not possible with the thorax intact to produce an isolated function of the intercostal muscles during expiration on account of the triangularis sterni, which in the dog is a strong muscle that is a continuation of the transverse abdominis.

To conclude the experiment, the diaphragm was freely opened and artificial respiration was continued a short time by compressing the oxygen bag that was put in communication with the tracheal cannula. By inserting the hand in the thorax the triangularis sterni could be felt to contract strongly during expiration. The sternal ends of the ribs and the costal cartilages were by its action vigorously drawn in an expiratory direction, but during inspiration the muscle was relaxed. While the thorax was intact, the last four ribs on both sides moved cephalad in inspiration and the intercostal spaces were widened.

With these experiments it seems clear how the integrative actions of the intercostals during inspiration are made to serve alternately for inflation and deflation of the lungs. During inspiration the scaleni and serrati postici, superior, supply the necessary cephalad anchorage for the entire length of the thorax; and in active expiration when the abdominal muscles are eliminated, the caudad anchorage for the bottom ribs is supplied by the serratus posticus inferior, and the caudad traction for the entire cuirass is supplied by the triangularis sterni. Until the triangularis sterni and those parts of the ribs to which it is attached were palpated during active expiratory efforts, the important function played by this sheet of muscle was greatly underestimated.

By these studies the conviction is gained that, in the orderly, integrated function of the scaleni and the intrinsic muscles of the thorax, we have a well ordered action that suggests the progress of a peristaltic wave, such as prevails along the gullet, where the action remains the same but the result is deglutition or vomiting as the gradient is caudad or cephalad. In the case of the intercostal muscles, their action is the same in inspiration and expiration, just as Vesalius said nearly four hundred years ago, but they aid expansion or constriction of the thorax according to the gradient, which is determined for inspiration by synchronous activation of the scaleni and serratus posticus superior and for expiration by the serratus posticus inferior, triangularis sterni, and abdominal muscles.

By this statement it is not intended to convey the idea that succession in the action of the intercostal muscles has been proved. In fact, my own experiments directed toward investigation of this question have thus far indicated that in inspiration all the intercostals are synchronously activated.

THE ESTIMATION OF NORMAL VITAL CAPACITY

WITH ESPECIAL REFERENCE TO THE EFFECT OF POSTURE *

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For controlling a contemplated experimental research on orthopnea we found it necessary to establish some standards for normal vital capacity in healthy persons in both the sitting and the lying position. In the literature many observations were found on the vital capacity under almost every other conceivable experimental condition, but although the statment is frequently made that a normal person can breathe more when sitting erect than when recumbent, we discovered no attempt to estimate the percental differences due to posture. Experimental investigation doubtless began with the work of John Hutchinson,[1] who gives data to show that the vital capacity is smaller in the supine position than in the erect. A few observations were made by us on individuals about the laboratory, and the results were found to vary considerably; that is, some could after a maximum inspiration expire as much lying as sitting, a few could expire more, and the majority were not able to do nearly so well lying as sitting. As these observations seemed to refute partially at least the idea that the vital capacity is always smaller in the lying position, it was decided to check the whole subject on a large series of normal people.

The investigation, entered into along the lines just described, widened into an inquiry as to the best basis for comparison in the estimation of vital capacity. Our data show very clearly that body surface, as determined by the linear formula of Du Bois, is a far more accurate and constant index of comparison than is height or weight, or certain measurements of the volume of the chest as recently advocated by Lundsgaard and Van Slyke.[2] Our data also seem to bear out the physiological fact, well established by Stewart[3] and others, that in animals the weight of the lungs bears a very definite and constant ratio to the skin surface.

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1. Hutchinson, J.: Med. Chir. Tr. **29**:137.
2. Lundsgaard and Van Slyke: J. Exper. M. **27**:65, 1918.
3. Stewart, G. N.: Am. J. Physiol. (In press).

We were able to make observations on 290 normal people—144 women and 146 men. The women were all healthy nurses, who had had a recent physical examination, and whose ages varied from 20 to 30 years. The men were practically all medical students, also ranging in age from 20 to 30 years; they had had a recent physical examination, and we were sure that they were normal. We were working with an intelligent lot, and we feel certain that the end result was the maximum effort in each case. When there was any doubt in our minds as to the accuracy of any determination, it was not included in our totals.

TABLE 1.—MALES: GROUPED ACCORDING TO WEIGHT IN KILOGRAMS

Weight in Kilos	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c.	Lying, C.c.			
55 to 65	49	4,272	4,017	255	5.9	13
65 to 75	61	4,661	4,440	221	4.7	17
75 to 85	26	4,974	4,674	300	6.0	5
85 to 95	10	5,379	5,109	270	5.0	7
Total.....	146	Average difference.....			5.5	42 or 28%

TABLE 2.—MALES: GROUPED ACCORDING TO HEIGHT IN CENTIMETERS

Height in Centimeters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c.	Lying, C.c.			
150 to 160	2	3,721	3,590	131	3.5	0
160 to 170	57	4,197	3,963	234	5.6	11
170 to 180	82	4,641	4,411	230	4.9	21
180 to 190	25	5,366	5,070	296	5.5	8
Total.....	146	Average difference.....			4.9	40 or 27%

TABLE 3.—MALES: GROUPED ACCORDING TO BODY SURFACE

Body Surface in Sq. Meters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c.	Lying, C.c.			
1.6 to 1.7	15	4,008	3,808	200	5.0	6
1.7 to 1.8	46	4,303	4,102	201	4.6	3
1.8 to 1.9	46	4,609	4,363	246	5.3	6
1.9 to 2.0	27	5,150	4,858	292	5.6	5
2.0 to 2.1	12	5,565	5,250	315	5.7	3
Total.....	146	Average difference.....			5.2	23 or 16%

METHOD OF STUDY

With an ordinary spirometer three estimations were made on each individual in the sitting position and three in the lying position. The largest amount which an individual expired sitting or lying, out of three attempts made in each position, was the figure which we used in computing our totals. All of the subjects were dressed in ordinary clothing, and no deductions were made in recording weights and there

was nothing taken from the height because of shoes. It is quite probable that some of the estimations in the case of the nurses were influenced by the fact that corsets were not removed.

Differences Due to Posture.—It will be seen from the tables that, when the vital capacities of all these 290 normal persons are averaged, there is for all groups approximately 5.5 per cent. less vital capacity in the recumbent position than in the upright. Some few breathed somewhat better lying; and some were able to expire about as much lying as sitting; but it is certain that about 80 per cent. of people breathe somewhere near 6.5 or 7 per cent. less in a reclining position, and the remaining 20 per cent. breathe either more or about the same.

TABLE 4.—FEMALES: GROUPED ACCORDING TO WEIGHT IN KILOGRAMS

Weight in Kilos	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c.	Lying, C.c.			
45 to 55	48	2,908	2,729	179	6.1	17
55 to 65	68	3,146	2,945	201	6.3	20
65 to 75	21	3,132	2,923	209	6.6	9
75 to 85	7	3,356	2,871	485	14.4	2
Total.....	144	Average difference.....			8.3	48 or 33%

TABLE 5.—FEMALES: GROUPED ACCORDING TO HEIGHT IN CENTIMETERS

Height in Centimeters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c	Lying, C.c.			
150 to 160	29	2,945	2,714	131	4.4	9
160 to 170	98	3,066	2,884	182	5.9	26
170 to 180	17	3,506	3,256	250	6.9	7
Total.....	144	Average difference.....			5.4	42 or 29%

TABLE 6.—FEMALES: GROUPED ACCORDING TO BODY SURFACE

Body Surface in Sq. Meters	Number Studied	Vital Capacity		Difference Between Sitting and Lying, C.c.	Percentage Difference	No. not Falling Within + or — 10% of Average
		Sitting, C.c.	Lying, C.c.			
1.4 to 1.5	11	2,688	2,520	168	6.2	3
1.5 to 1.6	45	2,939	2,804	135	4.6	7
1.6 to 1.7	54	3,108	2,926	172	5.5	9
1.7 to 1.8	21	3,246	3,046	200	6.1	6
1.8 to 1.9	15	3,400	3,148	252	7.4	1
Total.....	144	Average difference.....			5.9	26 or 18%

We attempted to discover whether differences in types of chest would account for these variations between lying and sitting, but the only thing which seemed to point to some different response was in the case of women of the rather obese type. The obese women sometimes breathed as much as 20 per cent. less lying than sitting. This is quite noticeable in Table 4, in which it will be seen that females weighing from 75 to 85 kilos averaged 14.4 per cent. less in the lying

position. We had no men in our series who were comparable to these females. Except for this disparity between the sitting and the lying position of fleshy females, it was found that, when vital capacity was taken in the two positions, all types of chest seemed to respond to the experimental conditions in much the same fashion.

Comparison with Height and Weight.—As to whether weight or height is the better index of comparison for the vital capacity was debated by John Hutchinson prior to 1846. He made observations on the vital capacity of 2,130 persons, all of whom were normal except sixty. These observations were made on people from all walks of life. It was his opinion that comparison of the vital capacity with the height of the individual was the most satisfactory method. However, Hutchinson as well as subsequent observers noted that the vital capacity in people of the same height varied tremendously, although it was noted by all that it was much more constant when compared with the height than with the weight.

Our data readily bear out the contention of John Hutchinson and subsequent workers that vital capacities of persons of the same weight vary widely (Tables 2 and 5). In the females there were 33 per cent. who did not fall within plus or minus 10 per cent. of the average when compared by weight, and there were 28 per cent. of the males who varied rather widely from their average. Our figures also agree with those of John Hutchinson in showing that a comparison of the vital capacity with the height is more accurate than with the weight. However, 27 per cent. of the females and 28 per cent. of the males when so compared missed the average by more than plus or minus 10 per cent. This error is more apparent than real, when comparison is made with height, for in those who missed the average of their respective groups, the variations were not great, while in the comparison by weight, many missed their group by hopeless differences.

Comparison with Chest Measurements.—Recently Lundsgaard and Van Slyke have contended that chests measured according to certain formulas and found to agree in size would more nearly have the same vital capacity than would the chest of persons of the same height. However, Peabody [4] has denied this contention of Lundsgaard and Van Slyke. Peabody's investigations show that persons of the same height have more nearly the same vital capacity.

Comparison with Body Surface.—Our data clearly demonstrate that it is not height or weight or chest measurements but body surface that is by far the most constant and exact standard for comparison. Dreyer [5] recently published data which seem to support this contention,

4. Peabody, F. W.: Oxford Med. **1**:399.
5. Dreyer, G.: Lancet **2**:227, 1919.

but the number of observations which he made is small. The data which West [6] accumulated on a comparison of vital capacity in normal individuals with the body surface agrees quite closely with our figures. In our observations (Tables 3 and 6) it will be seen that when the comparison is made with the body surface as estimated by the "linear formula" of Du Bois, only 18 per cent. of the females and 16 per cent. of the males missed the average for their respective group by plus or minus 10 per cent. Furthermore, there were scarcely any of either the women or the men who missed by more than 15 per cent. In addition it should be noted that most of those who did miss their respective group were the extremes in body surface—that is, those who had the smallest or those who had the greatest. For if we take the group of females whose body surface is from 1.5 to 1.7 square meters, which represents the size of approximately 80 per cent. of the women in our series, then we find that only 16 per cent. missed their respective group averages by plus or minus 10 per cent. In the case of the males, it will be seen that approximately two thirds fall in the two groups whose body surface is from 1.7 to 1.8 and from 1.8 to 1.9 square meters, and there were slightly fewer than 10 per cent. of these who missed their average by more than plus or minus 10 per cent.

The males in this group seemed to be distinctly more constant in the grouping of their vital capacity by body surface than were the females. This may be in part due to the fact that the females were not required to remove their corsets.

It will be seen from Tables 3 and 6 that in the case of females the vital capacity goes up about 175 c.c. with each increase of 0.1 square meter in body surface, while in the case of males the vital capacity advances about 350 c.c. for each gain of 0.1 square meter. Therefore, to get the normal total vital capacity of a woman of the age included in our group, it is only necessary to remember that a body surface of from 1.4 to 1.5 square meters indicates a vital capacity of 2,700 c.c., and that for each increase in body surface of 0.1 square meter, 175 c.c. must be added. In the case of a male, with a body surface of from 1.6 to 1.7, the average vital capacity is 4,000 c.c. For each increase in body surface of 0.1 square meter, add 350 c.c., which will give the approximate average for each group.

Then, from our series the advantage of reckoning the vital capacity from the body surface is apparent. There are, perhaps, few clinical methods of precision which do not have a greater range of error than plus or minus 15 per cent. After all, for comparative purposes one wants the lower range of normal; and while 16 per cent. of the males and 18 per cent. of the females missed their

6. West, Howard F.: Arch. Int. Med. **25**:306 (March) 1920.

respective average, only about half of those who missed the average of their respective group were below, and these are after all the only important ones to consider. So that, in reality, for comparison purposes only 8 per cent. of males and 9 per cent. of females missed their respective grouping by body surface by more than minus 10 per cent.

CONCLUSIONS

1. After computing the averages of all estimations on 290 normal men and women, we found that there was 5.5 per cent. less vital capacity in the lying than in the sitting position.

2. We noted also that about 80 per cent. of all inidviduals breathed 6 or 7 per cent. less when lying, and that 20 per cent, breathed about the same or more. We noted no difference in chest conformation to account for these variations. The only thing we did note which seemed to point to a different response from certain types of chest was in the case of obese women. In every instance the fleshy female breathed about 15 per cent. less lying than sitting.

3. According to our observations, individuals of the same sex and body weight have very great differences in their vital capacity; individuals of the same sex and height have more nearly the same vital capacity; while individuals of the same sex and body surface are surprisingly alike in their vital capacity. It was found that only about 8 per cent. of all males and about 9 per cent. of all females, when grouped according to body surface, missed their respective group average by more than minus 10 per cent.

4. From our totals we may conclude that a female from 20 to 30 years of age, with a body surface of from 1.4 to 1.5 square meters, has a vital capacity of 2,700 c.c., and for each gain of 0.1 square meter in body surface the vital capacity goes up about 175 c.c. A male from 20 to 30 years of age, with a body surface of from 1.6 to 1.7 square meters, has a vital capacity of about 4,000 c.c., and with each gain of 0.1 square meter the vital capacity goes up 350 c.c. From these data we can conclude that a normal male between the ages of 20 and 30 has a vital capacity of 2.5 liters per square meter of body surface, and that a normal female between 20 and 30 has a vital capacity of 2 liters per square meter of body surface.

THE CAPILLARY BLOOD PRESSURE IN ARTERIAL HYPERTENSION *

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Although the anatomy and physiology of the capillaries have been of interest to physiologists for many years and have been the subject of many investigations, their importance in the dynamics of the normal circulation and in the study of pathologic states is just beginning to be appreciated. The studies of Krogh [1] and Richards [2] on the response of the capillaries to the functional needs of the tissues; those of Dale [3] and Cannon [4] on the importance of the capillary mechanism in shock; the researches of Weiss [5] and his co-workers on the morphology of the capillaries and the character of the capillary flow in disease; and the studies of Kylin [6] and Danzer and Hooker [7] on the capillary blood pressure have within the last few years pointed out how essential a knowledge of the capillary function is to the clinician in his study of disease. The concept that the cardiovascular system is primarily adapted to maintain the blood flow in the capillaries, where the exchange of gases, food elements and waste between the tissues and the blood takes place, is a very fundamental one and one that cannot be overemphasized. It must further be recalled that the capillaries themselves play an active part in the maintenance of an adequate blood supply to the tissues, that they exhibit contractility and dilatability in response to nervous and metabolic stimuli and so assist in regulating the blood flow according to the needs of the tissues.[8]

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* From the Medical Division of the Montefiore Hospital for Chronic Diseases.

1. Krogh, A.: The Supply of Oxygen of the Tissues and the Regulation of the Capillary Circulation, J. Physiol. **52**:457 (May) 1919; Studies on the Capillariomotor Mechanism. I. The Reaction to Stimuli and the Innervation of the Blood Vessels in the Tongue of the Frog, J. Physiol. **53**:399 (May) 1920.

2. Richards, A. N.: Kidney Function, Am. J. M. Sc. **163**:1, 1922.

3. Dale, H. H.: Capillary Poisons and Shock, Bull. Johns Hopkins Hosp. **31**:257, 1920.

4. Cannon, W. B.: A Consideration of the Nature of Wound Shock, J. A. M. A. **70**:611 (March 2) 1918.

5. Weiss, E., and Dieter, W.: Die Strömung in den Kapillaren und ihre Beziehung zur Gefässfunktion, Zentralbl. f. Herz & Gefässkrankheiten **12**:295, 1920.

6. Kylin, E.: Studien über das Verhalten des Kapillardruckes, insbesondere bei arteriellen Blutdrucksteigerungen, Zentralbl. f. inn. Med. **41**:368, 1920.

7. Danzer, C. S., and Hooker, D. R.: Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer, Am. J. Physiol. **52**:136 (May) 1920.

8. Hooker, D. R.: Evidence of Functional Activity on the Part of the Capillaries and Venules, Physiol. Rev. **1**:112 (Jan.) 1921.

In this study we have been particularly interested in the rôle which the capillaries play in the maintenance of the peripheral resistance to the blood stream, and consequently in the etiology of hypertensive states. The problem of hypertension and its relationship to kidney disease still remains unsolved in spite of innumerable searching studies that have been made. Opinion has veered from the extreme view that hypertension is always a result of kidney disease to the opposite extreme that all kidney disease is secondary to hypertension. Both schools still have their advocates. From the maze of facts and theories that have surrounded the subject, one thesis may be granted as established—that the syndrome of hyperpiesia or essential hypertension may exist without any evidence of nephritis. Whether "nephritic hypertension" is a late stage of this or quite a different syndrome is unknown. Blood pressure studies have been singularly unilluminating in clearing up the matter. We have learned to appreciate that brachial blood pressure readings are very variable and that in many instances they depend on the degree of contraction of the arterioles. That the capillaries themselves may be concerned in the maintenance of this pressure was first brought out forcibly by Dale and Cannon, who showed that a paralytic dilatation of the capillaries may cause a great fall in blood pressure, even when the arterioles are contracted. The reverse side of the picture, namely, that the capillaries may themselves be a factor in the maintenance of high arterial pressures, is suggested by some of the studies of Kylin and of Weiss.

Kylin,[8] using an instrument something like Danzer and Hooker's, has made some very interesting observations on the capillary blood pressure in hypertension and nephritis. His observations are open to question because he used the cessation of the capillary blood flow as the criterion by which he measured the capillary pressure and also because his figures for normal readings are uniformly low—about 10 mm. Hg. In glomerular nephritis he found the capillary pressure abnormally high in 100 cases investigated, but in benign nephrosclerosis with hypertension it was always normal. He studied twenty scarlet fever convalescents daily and found in some a marked increase in capillary pressure. In three of these patients a typical glomerular nephritis developed with albumin, casts and red cells in the urine a few days after the capillary pressure had risen. The nephritis set in when the capillary pressure had reached about 23 mm. of mercury. The highest capillary pressure obtained ranged from 40 to 55 mm. of mercury. In a more recent article,[9] written in English, he summarizes the results of

9. Kylin, E.: Brief Notes on Hypertonia and Kidney Disease, Acta Med. Scandin. **55**:368, 1921.

his studies as follows: There are two types of hypertension. The nephrosclerotic hypertension is an arterial, the glomerulonephritic, a capillary hypertension. In the first form the brachial blood pressure is much more labile than in the latter. The hypertension is not the result of the kidney disease, but the glomerulonephritis is a manifestation of a diffuse capillary injury caused by the toxins of certain acute infectious diseases. Some of Weiss'[10] observations seem to confirm these views. He noted an increase in the number and a change in the appearance of the capillaries of the nail-bed in acute, as well as in chronic nephritis. They were longer and more convoluted than normal.[11] These observations were confirmed by Thaller and Draga [12] but disputed by Schur.[13]

With these studies in mind we studied a series of patients with hypertension in the wards of the Montefiore Hospital.

We employed the microcapillary tonometer described by Danzer and Hooker [7] for our determination of the capillary blood pressure. It is the most satisfactory instrument that has been devised for this purpose. In principle it resembles the instrument which Roy and Brown [14] devised in their studies on the capillaries of the frog. Lombard's [15] observation that the human capillaries could be visualized by observing the skin through a microscope after a drop of oil or glycerin had been applied to it was the next step in the development of the technic. Kraus [16] followed this lead and studied the pressure of human capillaries, using a magnification of 10 diameters. It remained for Danzer and Hooker to develop a practical, convenient technic, and to introduce the principle that the cessation of the blood flow in the capillaries, rather than the disappearance of the capillaries marks the proper pressure at which the reading should be taken.[17]

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10. Weiss, E.: Beobachtung und microphotographische Darstellung der Hautkapillaren am lebenden Menschen, Deutsch. Arch. f. klin. Med. **119**: Heft 1 and 2, 1916.

11. Weiss, E.: Das Verhalten der Hautkapillaren bei akuter Nephritis, München. med. Wchnschr. **63**:925, 1916.

12. Thaller, L., and v. Draga, E.: Zur diagnostischen Verwertbarkeit der mikroskopischen Hautkapillarenuntersuchung am lebenden Menschen, Wien. klin. Woch. **30**: No. 22, 1917.

13. Schur, H.: Mikroskopische Hautstudien am lebenden, Wien. klin. Woch. **32**:1201, 1919.

14. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variations in the Arterioles, Capillaries and Smaller Veins, J. Physiol. **2**:323, 1879.

15. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries and Small Veins of the Human Skin, Am. J. Physiol. **29**:335, 1912.

16. Krauss: Der Kapillardruck, Sammlung klin. Vorträge Inn. Med. No. 237-239, 315, 1914.

17. For a critical survey of methods to determine capillary pressure see Friedenthal, Ztschr. f. exper. Path. & Therap. **19**:2, 1917.

We followed the method of Danzer and Hooker, as outlined in their article. All readings were taken with the hand at heart level and the patient in a sitting posture, at a room temperature of 20-25 C. After the first few observations, we did not scrub the skin of the finger before making our readings, for we found it unnecessary and did not wish to introduce a possible complicating factor. Leonard Hill [18] has questioned the accuracy of this method. He states that the true measure of the blood pressure in the capillaries is that pressure which, when applied, will momentarily check the flow of blood in the capillaries, and that the pressure which will completely check the flow is equal to the pressure in the arterioles which supply the area compressed, because of the backing up of pressure in the occluded vessel. This is undoubtedly true. However, we have followed Danzer and Hooker's procedure of taking the reading as one does a blood pressure reading, i. e., noting the point at which the capillary flow returns as the pressure which has stopped the flow is released. With the drop in pressure, the blood first flows sluggishly through the capillaries but suddenly quickens to a rapid stream. This we have taken as the capillary pressure, and to this Hill's objections do not apply. Hill's second objection is that with this method, the pressure factor dependent on the resistance of the skin to compression is not excluded. As a matter of fact, by a method of his own he obtains very low readings for capillary pressures, from 2 to 5 cm. of water. Our observations seem to indicate that the resistance of the tissues does not appreciably modify the reading. We have examined many patients who exhibited marked atrophy of the skin in the area studied, as well as many whose skin was normal and others with quite a horny epidermis. The readings obtained did not vary according to the condition of the skin. Moreover in several patients with vasomotor disorders of the extremities we obtained a normal reading—about 20 mm. mercury on one day, and a very low reading—from 2 to 3 mm. mercury on another day. The latter reading is so low as to practically exclude the resistance of the skin as a factor.

It is well known that venous stasis will induce an elevation of the capillary pressure. We were careful, therefore, to exclude this factor in the cases studied. The observations detailed in the following table were made on patients whose systolic pressure was 180 mm. Hg. or over, selected at random in the wards of the Montefiore Hospital. For five of the cases we are indebted to the courtesy of Dr. H. J. Wiener, who permitted us to examine them in his Metabolism Division of the Vanderbilt Clinic.

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18. Hill, L.: The Capillary Blood Pressure, J. Physiol. **54**:xxiv, 1920; ibid. **54**:xciii,, 1921; Hill, L., and McQueen, J. M.: The Measurement of the Capillary Blood Pressure in Man, Brit. J. Exper. Path. **2**:1, 1921.

TABLE 1.—Results of Examination of Twenty-Three Cases

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
1. (A. G.)	M	55	Hypertension, chronic lead poisoning ?	No hypertrophy of heart; aortic second sound accentuated; thickening and tortuosity of temporals; slight of radials	1.023 Alk. No albumin No casts	39.0	Urea N.....10.5 Uric A..... 1.9 Sugar.....97	130/90-95	R-4 27.0 25.0 30.0 23.5 31.0 27.0 24.0 29.0 40.0 L-3 21.5 23.0 30.0 L-4 33.0 35.0 41.0 34.0 L-5 30.0	More looping of the venous arms than normal; many small fine capillaries with one small fine convolution present
2. (M. G.)	M	58	Hypertension, chronic nephritis	Cardiac hypertrophy; 2 attacks of hemiplegia; headaches, shortness of breath, swelling of eye lids; Wassermann negative	Alb. ++ Many casts	32.0 36.0	Urea N.....15.0 Uric A..... 3.1	230/128 235/120	30.0 27.0 27.0 30.0 R-3 43.0 45.0 46.0 R-5 36.0 27.0 38.0 32.0 L-3 38.0 48.0 L-5 44.0 28.0 27.0 33.0 36.0	Capillaries long, few looped
3. (S. W.)	M	50	Hypertension, chronic nephritis, diabetes	Cardiac hypertrophy; albuminuric retinitis, shortness of breath, swelling of feet; left chest tapped a number of times, bloody fluid withdrawn	Marked trace of albumin Many granular casts	40.0 32.5	Urea N. 5/25/21.....17.5 8/21/21.....27.4 12/5/21.....25.4 Uric A..... 2.5	244/150	35.0 40.0 53.0 49.0 R-3 85.0 60.0 50.0 R-5 41.0 43.0	Capillaries irregularly convoluted; subpapillary plexus seen

4. (M. L.)	F	58	Hypertension, chronic nephritis, arteriosclerosis	Cardiac hypertrophy; right hemiplegia; thickened tortuous vessels; Wassermann negative	Alb. trace Granular casts	20.0	Urea N.....13.5 Uric A..... 1.3 Creat..... 4.2	216/120	L-3 40.0 20.0 38.0 31.0 33.0 38.5 30.0 32.0 49.0 46.0 L-4 40.0 37.0 R-3 14.0 11.0 14.0 12.0 13.0 39.0 83.0 90.0 R-2 65.0 47.0	Left: capillaries very long, in several layers, not tortuous. Right: (hemiplegic), capillaries long, wider, some wound
5. (Ph. D.)	M	61	Hypertension, chronic nephritis, arteriosclerosis, emphysema	Cardiac hypertrophy, adv. thickening and tortuosity of vessels; Wassermann negative; high blood pressure since October, 1918	Alb. and casts	18.0	Urea N.....11.4 Uric A..... 5.1	212/110	R-3 40.0 46.5 45.0 37.5 54.5 52.0 36.0 R-4 52.5 R-5 38.0 L-3 36.5 39.0 41.0 31.0 39.0 35.0 L-4 39.0 39.5 40.0 L-2 50.0 47.0 L-5 45.0	Very many convoluted capillaries Long narrow capillaries Capillaries looped, longer than normal, (hemiplegic side) Very many capillaries, looped
6. (B. H.)	F	52	Hypertension, chronic nephritis and auricular fibrillation	Cardiac hypertrophy; attacks of decompensation	Alb. and casts	41.0	Urea N.....12.6 Uric A..... 2.1 Sugar.....119	238/110	L-3 66.0 70.0 L-5 70.0 R-4 63.0 48.0	Capillaries are long, parallel, regular, venous end thick, many subpapillary plexuses (venous)
16. (M. L.)	M	39	Hypertension, chronic nephritis	Heart normal; Wassermann negative; high blood pressure since April, 1921	1.012-1.027 Occasional hyalin casts	45.0	Urea N.....23.8 Uric A..... 1.95	216/120	24.0 45.0 60.0 22.0 60.0	Very long, straight and looped capillaries with engorged venous ends

R, right hand; L, left hand; figures 2, 3, etc. indicate the finger of the hand. Thus. R-4 means the fourth finger of the right hand.

TABLE I.—Results of Examination of Twenty-Three Cases—(*Continued*)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
17. (C. G.)	F	59	Hypertension, chronic nephritis	Vertigo, dizziness, headaches past six years; slight cardiac hypertrophy; slight accentuated second sound and pulmonic second sound; blood pressure 235/140	1.010 (24 hr.) 1.011 Alb. 0	....	N.P.N.....45.5 Urea N.....39.0 Uric A..... 2.8 Creat..... 1.37	196/120	35.0 45.0 26.0 65.0 60.0 65.0 56.0 42.0 52.0 44.0	Capillaries numerous and tortuous
21. (F. W.)	M	69	Arteriosclerosis extensive, with calcification of small arteries and gangrene of leg	Diabetes (?); headaches and dizziness; cardiac hypertrophy; amputation of left leg one year ago for gangrene; cerebral hemorrhage with high blood pressure four years ago	1.005-1.018 Alb. trace No casts Many W.B.C.	26.5	Urea N..... 9.1 Uric A..... 3.4 Creat..... 1.5 Sugar.....127.0	164/90	L-4 21.0 35.0 27.0 27.0 25.0 L-5 41.0 29.0 33.0 31.5 29.0 L-2 40.0 40.0 40.0 23.0 R-4 26.5 26.5 R-2 42.0 36.5 36.5	Capillaries long, looped, irregular, many layers, subpapillary plexus; very irregular architecture; streaming at 0 mm.; venous end thick
? (A. G.)	M	59	Hypertension, diabetes mellitus	Cardiac hypertrophy (slight); mild diabetes; with few symptoms; Wassermann negative	1.015-20 Alb. neg. Sugar trace No casts	45	Urea N..... 18.9 Uric A..... 2.5 Sugar..... 228	174/110	L-5 15.0 16.0 18.0 14.0 14.0 L-4 18.0 21.0 17.5 L-2 16.5 16.5 17.5 L-3 17.5 18.5 14.0 17.0	Capillaries increased, no straight loops, curved but not entwined; venous ends somewhat engorged Very greatly elongated and curved; engorged venous ends Many elongated tortuous capillaries Same

									R-5	15.0 12.0 14.0 16.5	Tortuous and elongated
									R-4	22.0 27.0 19.0 20.0 16.0	Massive capillaries, some tremendously engorged
									R-2	22.0 13.0 16.0	Many large and small capillaries, normal in appearance
8. (J. S.)	M	44	Hypertension, arteriosclerosis, emphysema, chronic valvular disease, mitral stenosis	Cardiac hypertrophy; aortic second sound ++; slight sclerosis, temporal artery; clubbed fingers; Wassermann negative	1.014-20 Alb. 0 to V. F. T. No casts	30	Urea N.....15.4 Uric A..... 1.7	164/94 184/100		8.5 4.0 4.0 10.0 5.0	Very many capillaries to field
9 (I. R.)	F	69	Hypertension, general arteriosclerosis, auricular fibrillation	No cardiac hypertrophy; amputated left foot for gangrene; blood pressure 170 on admission	No albumin or casts	4 32.5	Urea N.....14.7 Uric A..... 1.3 Sugar.....02	145/90	L-3	4.0 2.0 6.0	Very many capillaries, most in long loops, few with convolutions; streaming at 0; subpapillary plexus visible
10. (P. K.)	F	60	Hypertension, arteriosclerosis	Cardiac hypertrophy; slight thickening of radials; left hemiplegia three years ago; Wassermann negative	Alb. ++ R. B. C. No casts (cystitis)	9/9/21 12.5 10/22/21 20.0	Urea N.....11.9	175/85	R-4 R-3	5.0 7.0	Capillaries looped, irregularly arranged Hemiplegic hand not examined
11. (B. S.)	F	55	Hypertension, arteriosclerosis	Cardiac hypertrophy; left hemiplegia three years ago; Wassermann negative; blood pressure 250/120 one year ago; second stroke with death; necropsy	1.010-1.016 Alb., faint trace No casts	25.0	Urea N.....27.3	180/95	R-3 R-4 R-2	15.0 17.0 15.0 12.0 9.0 7.0 11.5 7.5	Capillaries long, irregular, tortuous; "granular" streaming at 0; extensive subpapillary plexus with capillaries running into it
12. (P. F.)	M	61	Hypertension, arteriosclerosis, emphysema	Slight cardiac hypertrophy; sclerosed arteries; clubbed fingers; Wassermann ± —	1.011-22 Alb. ++ Sugar ++ No casts	17.5	Urea N.....10.8 Uric A..... 2.8 Sugar.....101.0	180/100	9/16/21 L-5 L-2 	20.0 20.0 17.0 15.0 14.0 73.0 68.0 67.0 66.0 62.0 56.0 47.0 37.0 6.0 24.0	Almost normal looking Extremely convoluted; great number flowing at 75; flow visible at 0; streaming both "granular" and rapid

TABLE I.—Results of Examination of Twenty-Three Cases—(*Continued*)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
12. (P. F.) (Continued)	..	..	.....	.....	.....	.....	.....	158/85	10/10/21: L-2 16.0 14.0 10.0 L-5 13.0 11.0 10.0 20.0 16.0 11.0 R-4 20.0 R-5 6.0 R-2 12.0	Some capillaries very large; many convoluted many times; irregular in arrangement; subpapillary plexus visible
13. (B. P.)	F	63	Hypertension, emphysema, diabetes mellitus	Moderately enlarged heart, aortic second sound + +; macroscopic cap. pulse; both legs amputated for diabetic gangrene 5 years ago; (X-ray calcified arteries); Heberden's nodes on all fingers; blood pressure, 180/146 in 1919, 198/80 in 1921; Wassermann negative	1.011-1.022 Alb. + + Sugar + + Hyalin and granular casts	7.5	3/3/21: Urea N.....15.7 Sugar.....130 10/19/21: Urea N.....36.6 Sugar.....152.0 12/7/21: Urea N.....22.4 Sugar.....122.0	198/80 210/85	R-3 26.0 27.0 22.0 35.0 R-4 13.0 15.0 R-3 21.0 R-2 23.0 21.5 10.0 14.0 11.0 L-4 14.5 11.5 L-3 17.0	Very many small fine capillaries Longer and more tortuous than normal Very long capillaries; subpapillary plexus visible Long, somewhat convoluted
14. (M. G.)	F	47	Hypertension, chronic nephritis (?)	Cardiac hypertrophy; aortic second sound greater than pulmonic second sound; systolic at apex and base; blood pressure 220/120; Wassermann negative	10/10/13 Alb. + +	63 1 hr. (intravenous)	N.P.N.....38.6 Urea N.....29.4 Uric A..... 3.6	204/140	L-3 11.0 6.0 19.0 7.0 11.0 29.0 25.0 13.0 L-2 17.0 23.0 21.0 22.0 13.0 16.5 L-4 36.0 28.5	Capillaries very long, extremely looped Very long, looped Very long and convoluted, few loops

									27.0 10.0 25.0 17.5 L-2 29.0 29.0 17.0 L-3 10.0 R-3 30.0 32.0 26.0 R-4 22.0 16.0 15.0 13.0 6.0 15.0 R-5 17.0 11.0 10.0	Massive capillaries with many convolutions Very wide and long Very long, no loops
15. (N. D.)	F	50	Hypertension	Cardiac hypertrophy; aortic second sound ++ greater than pulmonic second sound; blood pressure 225/120 to 190/100; normal arteries; normal eyegrounds	1.011-20 Alb. 0 to V. F. T. No casts Sugar +	73	Urea N.....7.7 Creat .....0.9 Sugar.....94	208/100	13.0 7.5 17.0 7.0 7.0 8.0 7.0	Capillaries numerous, long; several layers deep, moderately tortuous
18. (S. S.)	M	62	Hypertension, asthma, chronic bronchitis, myocardial degeneration	"Asthmatic attacks"; no enlargement of heart; headaches; secondary anemia	1.010-14 No alb. or casts	47.5	Urea N.....19.4 Uric A..... 3.9	174/72	R-4 11.0 4.0	Capillaries extremely long; crowded together with many convolutions; granular streaming in most at 0; great number of anastomoses
19. (F. G.)	F	48	Hypertension, chronic nephritis, uremia	Persistent vomiting; loss of weight and strength; headaches; cardiac hypertrophy; secondary anemia; Wassermann + ±	1.007-1.030 Alb. marked trace Rare gr. casts W. B. C. Some R. B. C.	6	10/26: Urea N.....126.0 Uric A..... 9.4 Creat..... 7.4 10/31: Urea N.....112.0 Uric A..... 11.6 11/11: Urea N.....140.0 Uric A..... 7.1	195/104	R-3 5.0 5.0 R-2 10.0	Capillaries very long, no loops; flowing at 0 with granular streaming
20. (S. S.)	M	55	Hypertension, cardiac hypertrophy, emphysema; chronic nephritis	Edema of legs, dyspnea, abdominal distention; Wassermann negative	1.024-1.031 Alb. trace Hyalin and granular casts	40	Urea N.....23.0	226/100	9/19/21: L-3 31.5 17.0 19.5 12.0 23.0 R-4 22.5 18.0	Capillaries long, many with one or more loops, quite irregular; some capillaries very thick

TABLE 1.—Results of Examination of Twenty-Three Cases—(*Continued*)

Number	Sex	Age	Diagnosis	Clinical Facts	Urine	Kidney Function (2 Hr.)	Blood Chemistry, Mg. per 100 C.c.	Blood Pressure	Capillary Pressure	Capillary Appearance
20. (S. S.) (Continued)	.	..	.....	.....	.....	.....	.....	.....	18.0 15.5 19.5 22.5 R-5 17.0 26.5 23.5 13.0 R-2 38.0 25.0 26.0 205/110 10/13/21: R-4 28.5 21.0 25.0 23.0 L-3 26.0 29.0 25.0 L-4 34.0 27.0 21.0 38.0	
22. (G. F.)	M	68	Hypertension, chronic nephritis, emphysema	Cardiac hypertrophy; aortic second sound +; old left hemiplegia; blood pressure 260/140 to 210/120; no cardiac symptoms	1.016-1.017 Alb. trace Few hyalin casts	Less than 5	Urea N.....17.6 Uric A..... 1.6	210/120	R-3 26.0 30.0 L-4 11.0 4.0 0.0	Capillaries long, many convoluted; no flow at 0 mm. in many capillaries; many rows of capillaries visible
23. (B. J.)	F	45	Hypertension, general arteriosclerosis, chronic nephritis	Left hemiplegia three years; headaches; cardiac hypertrophy; aortic second sound +; old hemorrhages in fundi	1.008 Alb. ++ Few granular casts	21	Urea N.....14.1	238/138	R-4 24.0 24.0 19.0 R-5 23.5 16.5 20.0 19.0	Capillaries very long and thin; very many to field; no convolutions; subpapillary plexus visible

Danzer and Hooker determined that the normal capillary pressure ranged from 18 to 22 mm. of mercury. They found that in any individual most of the readings on different capillaries varied from 6 to 7 mm. of mercury, although in many capillaries the difference was greater. They, however, discarded the very high and the very low readings and took as the capillary blood pressure the average of those which did not exceed this variability. We, too, as is apparent from

TABLE 2.—SHOWING THE DISTRIBUTION OF THE READINGS OF CAPILLARY PRESSURE *

	Mm. Mercury								
Case	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Patients With Hypertension:									
1	..	..	11	5	1	..	..	..	..
2	..	..	7	6	5	..	..	..	..
3	..	..	..	2	4	2	..	..	1
4	..	6	1	9	3	..	1	..	2
5	..	..	..	13	6	3	..	..	..
6	..	..	..	..	1	..	4	..	..
16	..	..	2	..	1	2	..	..	..
17	..	..	1	1	3	3	2	..	..
21	..	..	..	..	..	..	..	..	..
7	..	23	4	..	..	..	..	..	..
8	5	..	..	..	..	..	..	..	..
9	3	..	..	..	..	..	..	..	..
10	2	..	..	..	..	..	..	..	..
11	3	5	..	..	..	..	..	..	..
12a	4	2	1	1	1	4	14	..	..
12b	3	9	..	..	..	..	..	..	..
13	1	7	6	1	..	..	..	..	..
14	6	15	13	2	..	..	..	..	..
15	5	2	..	..	..	..	..	..	..
18	1	1	..	..	..	..	..	..	..
19	3	..	..	..	..	..	..	..	..
20a	..	9	7	2	..	..	..	..	..
20b	..	..	9	2	..	..	..	..	..
22	2	2	1	..	..	..	..	..	..
23	..	4	3	..	..	..	..	..	..
Patients With Normal Blood Pressure:									
24	..	7	12	1	1	..	..	..	..
25	..	21	20	..	..	..	..	..	..
26	..	..	18	1	..	..	..	..	..
27	3	11	9	3	1	..	..	..	..
28	11	..	..	..	..	..	..	..	..
29	1	8	4	..	..	..	..	..	..
30	3	11	1	..	..	..	..	..	..
31	..	3	..	..	..	..	..	..	..
32	6	15	5	3	..	..	..	..	..
33	3	12	5	..	..	..	..	..	..
34	..	..	3	..	..	..	..	..	..
35	..	..	2	2	1	..	..	..	..

* Cases in which only very few readings are recorded are ones in which all of the capillaries in the microscopic field exhibited a reappearance of the blood flow at the same pressure. Early in the work the number of capillaries observed were not counted.

Table 1, encountered wide differences between the pressure readings in different capillaries of the same individual. This variability is so constant in most cases that we feel it cannot be ignored. It has long been known that there is a great variation in the degree of filling of different capillaries and in the rate of their blood flow. Roy and Brown drew attention to this in 1879 and many others have subsequently noted the same phenomenon. It remained for Krogh to point out the relationship of this variability of flow to the functional needs of the

tissues. With the inconstancy of flow there must be a corresponding fluctuation of the capillary pressure. Thus the variations in the readings which we observe are of real significance and should be recorded. We deem it wisest to record all of the observations. Because of the wide range of variability and the relatively small number of readings, an average would be deceptive. It is possible that the degree of variability of the readings in different individuals may have some clinical significance. That it is not due to errors of measurements is shown by the fact that successive readings on one capillary taken at the same sitting are usually quite constant.

It has been suggested that high readings are due to the fact that the capillaries on which such pressures are observed are seated more deeply in the tissues, or that some anatomic peculiarity is the determining factor. The following facts show that this does not usually obtain. By careful focussing of the microcope one can show that the capillaries giving high readings are often superficial. The size of the capillary bears no relationship to the pressure observed therein. Moreover, if the same group of capillaries is kept under observation for a period of time, or is studied on different days, marked variations in their pressure are observed. For instance, in Case 6 a group of four capillaries of varying shapes and sizes gave the following successive readings, the figures for all four capillaries at any one time being the same—45, 38, 52. Four days later the readings were 48, 49, 49, 55. On both days during the period of observation one of the four capillaries disappeared from view for several minutes at a time. On such occasions we were able to make it reappear by raising the pressure to 90 or 100 and quickly releasing it several times in succession. This acts, we believe, as a mechanical stimulus to the arterioles, capillaries and venules. In another patient (Case 26) the following note was made:

While the pressure in most of the capillaries in the microscopic field was 28, in one capillary there was but the slightest streaming of blood at 0. The pressure was raised to 90 and quickly released. Thereupon the microscopic field became markedly hyperemic and the pressure in most of the capillaries was 25. In the capillary in which the reading had been 0, the pressure now was 12.

We think that at times unlike pressures in different groups of capillaries are due to the fact that the arterioles supplying the groups exhibit different pressures or degrees of contraction. Case 25 may be cited as an example. Observations made on the fourth finger of the left hand passing from the left to the right side of the nail-bed, so that the first and last readings were made on capillaries separated by a distance of one centimeter, were as follows:

Left 8, 8.5, 10, 15, 20 Right
and again Left 10, 10, 14, 15.5, 17, 20 Right

It is clear from this discussion that the capillary pressure in the same and different vessels may vary from physiologic as well as from anatomic causes.

It is difficult to draw any final conclusions from a study of the tables. The cases fall into two groups—those with high capillary pressure and those with a low or normal capillary pressure. It is impossible to classify the patients clinically. Neither the history, the physical examination, nor the study of kidney function reveals any differential features. Similar urinary findings are common to both groups; in both we find low as well as normal phenolsulphonephthalein excretion. There is no difference in the pulse pressures in the two series. While it is true that on the average patients with a high capillary pressure exhibit a high diastolic blood pressure, there are sufficient exceptions to this rule to invalidate any supposition of a causal relationship between the two.

On further reflection these apparently vicarious figures find some theoretical justification. If Kylin's division of hypertensive states is a correct one, it may well be that those of our patients who showed kidney involvement with a low capillary pressure did not fall within the group exhibiting glomerulonephritis and general capillary disease. As a matter of fact necropsies in two of our cases support this belief. The following extracts from the autopsy protocols of Cases 11 and 19 give no evidence of a diffuse glomerulonephritis:

REPORT OF NECROPSY FINDINGS

Case 11.—Right kidney weighs 120 gm.; left, 80 gm. Capsule markedly adherent. Scattered large arteriosclerotic scars. On section the cortex varies in thickness, striations irregular, vessels prominent.

Microscopic examination reveals scarring with thickening and obliteration of the vessels in the depressed areas. Slight fibrosis of the glomeruli with some thickening of Bowman's capsule. In the scarred areas the glomeruli are fibrosed.

There is marked arteriosclerosis of the aorta, of the cerebral and coronary arteries. In the posterior wall of the left ventricle there is a large white scar. There is a large cystic area in the right occipitoparietal region, and a hemorrhage in the left internal capsule.

Case 19.—Each kidney weighs 50 gm. They are firmer than normal. Capsule adherent, leaving on removal a finely granular surface. The cut surface is pale and granular. The cortex is from 2 to 3 mm. in diameter. Striations are absent. Small vessels are prominent.

Microscopic examination shows a complete loss of normal architecture. Marked sclerosis of the larger vessels. Tubules are arranged in irregular groups and are dilated. Their cells are low, cuboidal, and the lumen is filled with exudate. There is a great deal of connective tissue with round cell infiltration. Most of the glomeruli have undergone a fibrous or hyaline change. A few still have a normal appearance, but even in these Bowman's capsule is much thickened.

Diagnosis: Primary contracted kidney.

When we recall that experienced clinicians have recognized the impossibility of diagnosing the anatomic lesion in the kidney from the clinical picture, particularly in chronic nephritis, we are in a position to understand why, in the cases we studied, we have been unable to predict which cases will exhibit a high capillary pressure as one of the manifestations of a glomerulonephritis. If our postulates hold true, however, and for confirmation we must await the postmortem examinations on appropriate cases, the estimation of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis, from other types of kidney disease. It is not, however, of value in the differentiation of nephritic from essential hypertension.

Another question which remains unsolved is whether the capillary hypertension contributes to the general arterial hypertension, or whether it is a concomitant phenomenon. It is well known that when, in patients with hypertension, particularly, serial blood pressure readings are taken, the final reading will often be considerably lower than the first one. Table 3 presents such a series of readings on the two groups of patients:

TABLE 3.

	Blood Pressure in Mm. Hg					Length of Observation, Min.	Drop in Systolic Blood Pressure, Mm. Hg
High Capillary Pressure							
Case 2	240/120	230/110	220/100	206/100	206/100	5	34
Case 3	206/120	204/120	210/120	202/120	200/110	10	6
Case 5	250/140	240/150	228/125	214/125	212/122	12	38
Low Capillary Pressure							
Case 7	180/110	184/106	184/110	180/110	180/110	10	0
Case 12	184/102	176/ 96	174/ 96	180/ 94	178/ 96	12	6
Case 8							
10/ 8/21	186/ 90	174/ 90	170/ 80	168/ 80	160/ 90	10	26
10/10/21	152/ 82	160/ 90	154/ 86	158/ 88	156/ 88	10	4
12/ 1/21	184/100	180/ 90	166/ 90	176/ 96	174/ 94	10	10
12/ 6/21	174/ 96	172/ 94	170/ 90	174/ 90	172/ 90	10	2

It is apparent that the blood pressure is equally unstable in both groups. Were the high capillary pressure a cause for the sustained hypertension, one might imagine that in such cases the blood pressure readings would be more constant.

Furthermore, were the connection a close one, one would expect the blood pressure to vary, *pari passu*, with the capillary pressure. We have observed this only in Case 12, where readings taken on different days at different levels of blood pressure revealed parallel changes in the capillary pressure. We must dispute the statement of Secher [19] that the capillary pressure, as a rule, follows the blood pressure. He cites one case in which wide fluctuations of the blood pressure were accompanied by parallel changes in the capillary pressure.

19. Secher, K.: Kliniske Kapillaerundesøgelser, Ugeskrift f. Laeger **83**:899, 1921.

The mechanism of a low capillary pressure is easily explained. A constriction of any blood vessel will be followed by a rise of pressure central to the constriction, and by a fall of pressure peripheral thereto. In hypertension, due to a contraction or a diminution of the lumen of the arterioles, the capillary pressure will be low. Thus it would seem that in most of our cases of hypertension there is a narrowing of the arterioles. A high capillary pressure will follow a dilatation of the arterioles or a constriction of the venules, or a high venous pressure due to stasis. It is not clear how disease of the capillaries themselves would lead to a high capillary pressure, particularly when we recall that arteriosclerosis of itself does not lead to a high arterial pressure. This is the weak point in Kylin's theory. It is conceivable that a lesion of the venous loop of the capillary might raise the pressure in the arterial loop, or that a stiffening of the endothelial tube due to disease might increase the pressure needed to check the blood flow in the capillaries.

That the appearance of the capillaries in our cases does not correspond to the accepted normal is evident from the table. We are not ready, however, to subscribe to Weiss' positive views as to the significance of these morphologic changes. We believe that the normal has not yet been sufficiently established. We have observed in normal individuals capillary pictures that correspond to descriptions of the capillaries characteristic of nephritis and arteriosclerosis. In general, it may be said, however, that the capillaries when diseased behave as do the arteries. They become long and, as a consequence, tortuous. This may be due to an organic change in the capillary or it may be as Lapinsky [20] pointed out, due to loss of tone following injury to the nerve supplying the area in question.

CONCLUSIONS

1. In patients with normal blood pressures the blood pressure in the capillaries of the fingers rarely exceeds 30 mm. of mercury.

2. Patients with hypertension fall within two groups that cannot be differentiated clinically. In the first group the capillary pressure ranges between 21 and 70 mm. of mercury, rarely higher and only very exceptionally lower. Most of the readings fall between 30 and 60. In the second group the capillary pressure falls within the range of normal, with a tendency to be low rather than high.

3. It is possible that patients who exhibit high capillary pressures are suffering from a general capillary disease with a glomerulonephritis as one of the manifestations. If this view is confirmed, the estimation

20. Lapinsky, M.: Studien über die lokale Blutzirculation im Bereiche gelähmter Nerven, Arch. f. Anat. & Physiol. (Physiol. Abtheil.) 477, 1899. Supplement.

of the capillary pressure may prove an important aid in the differential diagnosis of glomerulonephritis from other forms of kidney disease.

4. In essential hypertension the capillary pressure is low.

5. In any given individual varying pressures are usually observed in different capillaries. In patients with a normal capillary pressure the difference between the high and low readings is on the average 18 mm. Hg. In patients with a high capillary pressure this difference is on the average 36.6 mm. Hg. Thus the variability of the capillary pressure is greater in patients with high readings.

6. The variability of the capillary pressure depends on physiologic as well as on anatomic moments.

7. Mechanical stimulation of the capillaries will alter the blood flow, as well as the blood pressure within the capillaries.

AN ELECTROCARDIOGRAPHIC STUDY OF FIFTY PATIENTS DURING OPERATION*

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For a thorough understanding of the action of the heart, it is important that it be studied under various conditions of stress. This investigation was undertaken to determine whether there are any abnormalities in the mechanism of the heart beat, demonstrable by electrocardiography, during the period of anesthetization and surgical operation.

Heard and Strauss [1] reported a case of atrioventricular rhythm detected electrocardiographically in a patient still under ether following an operation. They state, "no other cases of nodal rhythm have been observed by us in a series of twenty-one cases in which electrocardiographic records have been taken during anesthesia." Levine [2] reported cases of acute cardiac upsets occurring in association with surgical operations. In two of his cases electrocardiographic tracings were made during attacks of paroxysmal auricular tachycardia while the patients were still under ether. These two reports were the only references to the subject found in the literature.

MATERIAL AND METHODS

This paper covers the study of fifty operations performed on forty-eight individuals on the surgical service of the Peter Bent Brigham Hospital during May and June, 1921. The cases were selected to the extent that the widest possible variety of conditions of age, type of anesthesia, cardiac condition, operative procedure, etc., were covered. They represent the more serious of the usual operative cases. The total time during which patients were under observation was seventy-five hours. During this period a total of 1,750 records were made. Electrodes of the type described by Cohn [3] were applied and preliminary tracings made before the beginning of anesthesia. By

* From the medical and surgical clinics of the Peter Bent Brigham Hospital.

1. Heard, J. D., and Strauss, A. E.: An Electrocardiographic Study of Two Cases of Nodal Rhythm Exhibiting R-P Intervals, Am. J. M. Sc. **75**:238, 1918.

2. Levine, S. A.: Acute Cardiac Upsets Occurring During or Following Surgical Operations, J. A. M. A. **75**:796 (Sept. 18) 1920.

3. Cohn, A. E.: A New Electrode for Use in Clinical Electrocardiography, Arch. Int. Med. **26**:105 (July) 1920.

means of an electric buzzer the anesthetist signaled to the electrocardiograph operator the moment at which anesthesia and operation were begun and ended, and also indicated any critical stages in the operation or in the patient's condition. By this means, tracings and operative procedures were correlated. Short records were made at intervals from the beginning of anesthesia until the time when the patient was ready to leave the operating table. On the average a tracing was made every two and one-half minutes. Graphic records were obtained for about 3 per cent. of the time the patients were on the table. The galvonometer string was watched for a much longer period than this, and any gross abnormality of rate or rhythm, lasting more than a few minutes, would have been detected. Most records were of Lead II, but occasionally, because of manipulations during operation in abdominal cases, it was necessary to use Lead I.

HEART RATES

The rate of the heart during operation is a matter of practical importance. Operators usually rely on the pulse rate as furnished by the anesthetist. In this study it was found that the heart rate, calculated from electrocardiographic tracings, in many instances was much higher than the count the anesthetist reported. The highest heart rate in this series was 217 beats per minute, occurring during the etherization of a child. The highest recorded pulse rate in this case was 180. In seventeen cases, or 34 per cent., the heart rate was twenty or more beats per minute faster than the highest recorded pulse rate. In nine cases, or 18 per cent., this discrepancy amounted to thirty or more beats. The most marked difference was in the case of a girl, who held her breath during the early stages of etherization. Her heart and pulse rates are shown in Figure 1. Discrepancies occurred with equal frequency under ether and gas-oxygen anesthesia. In certain of these cases there may have been an actual pulse deficit. In others the discrepancy might be explained by the fact that the pulse rates taken at five minute intervals did not catch short rises in rate shown by the more frequent electrocardiographic readings. Again, the highest rates and the most marked discrepancies occurred usually during the induction of anesthesia, when the pulse rate was taken by a nurse from the ward. During the period of operation, a trained anesthetist took the readings, using the temporal artery.

These observations show that the anesthetist's chart of pulse rate cannot be taken, in many instances, as a record of heart rate. For those cases in which it is important that the operators have accurate information, the rate should be obtained from the apex beat. This is easily done by strapping a stethoscope over the precordium, using tubing of sufficient length to reach the anesthetist. Another accurate method,

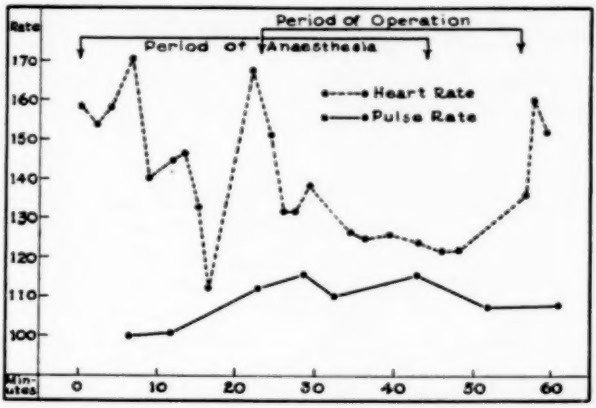

Fig. 1.—Upper line shows the heart rate as determined from electrocardiograms; lower line, the pulse rate as recorded by the anesthetist.

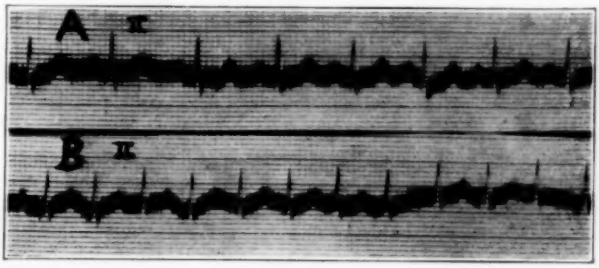

Fig. 2.—Case 7. Operation, fixation of uterus. A. Tracing taken twenty-six minutes after beginning of operation; rate 104, rhythm normal. B. Taken four minutes later than A; rate 164, paroxysmal tachycardia.

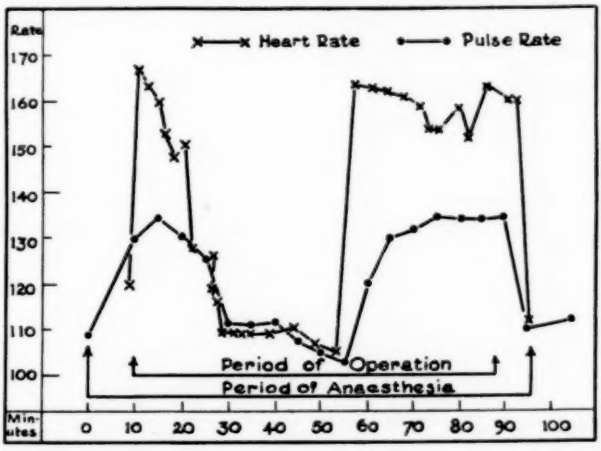

Fig. 3.—An instance of paroxysmal tachycardia unsuspected by the operating staff.

used in the head operations of this series, is to count the pulsations in the brachial artery as heard in the auscultatory method of obtaining blood pressure records.

ABNORMALITIES OF RHYTHM

Paroxysmal Tachycardia.—One patient, a woman, 80 years of age, showed this type of arrhythmia. The electrocardiogram appears in Figure 2, and the heart and pulse rates in Figure 3. The first sharp rise in rate, from 120 to 167, occurred during the half minute or so required to change from one lead to another. Without the electrocardiograph, this abnormality would have gone unrecognized, for the anesthetist noted only a rise of pulse rate to 135. The fast rate was unaccompanied by any adverse change in the patient's condition.

Premature Beats.—In eleven cases, premature beats were recorded. They were ventricular in origin in seven cases, and auricular in four. It should be stated, however, that two of the eleven showed premature beats in the preliminary tracings and in another there was a clear past history of premature systoles. One case which showed paroxysmal auricular tachycardia and premature beats on entrance to the hospital, ten days before operation, showed no abnormality during operation. During the ten day interval he had been on digitalis. The records of eight of the eleven cases showed only one or two premature beats. In two cases, premature beats occurred for short periods as often as every third beat. In none did the anesthetist note the irregularity. The time relations of the premature beats to the operation are shown in the upper part of Figure 4.

Sinus Arrhythmia.—The occurrence of well marked sinus arrhythmia was noted in three cases.

DISTURBANCES IN CONDUCTION

Delayed auriculoventricular conduction, with a lengthening of the P-R interval from 0.2 to 0.24 second, occurred in one patient during an operation for the ligation of a thyroid artery. Krumbhaar [4] reported forty-seven cases of toxic goiter in which tracings were taken before and after operation; two of these showed a delay in conduction time after operation. In regard to disturbances in the branches of the conduction apparatus, it is worthy of note that in our series, no case showed a prolongation of the Q R S interval. One case showed a widened Q R S complex (0.1 second) in the preliminary tracing, but it did not increase during the operation. The patient died eight days later from bronchopneumonia and pulmonary embolism.

4. Krumbhaar, E. B.: Electrocardiographic Observations in Toxic Goiter, Am. J. M. Sc. **155**:175, 1918.

There was no evidence of heart failure, but at the necropsy an area of fibrous myocarditis 1×2 cm. in size was found in the wall of the left ventricle.

DISLOCATION OF THE PACEMAKER

The chief interest of the study was found to lie in the frequent displacement of the cardiac pacemaker, as evidenced by changes in the shape, direction and position of the P wave (auricular complex). Fifteen of the cases, or 30 per cent., showed some variation in the

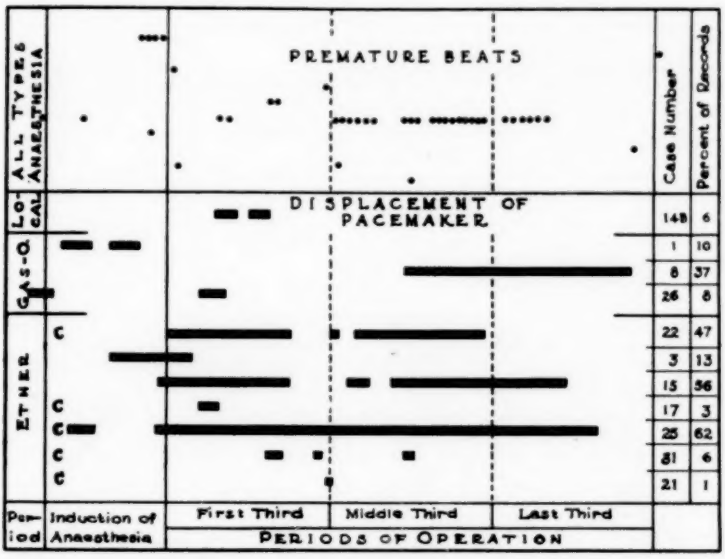

Fig. 4.—The chart illustrates the period during which premature beats and displacement of the pacemaker occurred. The upper portion is for the ten cases which showed premature beats. Each dot represents one such beat. The lower portion is for the eleven cases which showed marked abnormalities of the P waves. They are grouped according to the anesthetic used. In the ether group the letter C indicates those receiving ether by the Connell apparatus. On the right the first column of figures gives the case number and the second column the percentage of records which showed the abnormal rhythm. The length of the black line is, in each case, a rough measure of the percentage of records which showed the abnormality.

P wave not present in the preliminary tracings. In three of the cases, the abnormality consisted only in a shortening of the P-R interval of 0.04 second or more. This shortening was not due to an increase in rate. In one of the cases there was only a flattening of the P waves. Various explanations for such flattening have been discussed by Wil-

son,[5] e. g., diminution in contractility of auricles, interference of two rhythms, changes in the path of the contraction wave over the auricles and changes in the location of the pacemaker. In the remaining eleven cases the tracings showed more marked variations of the auricular

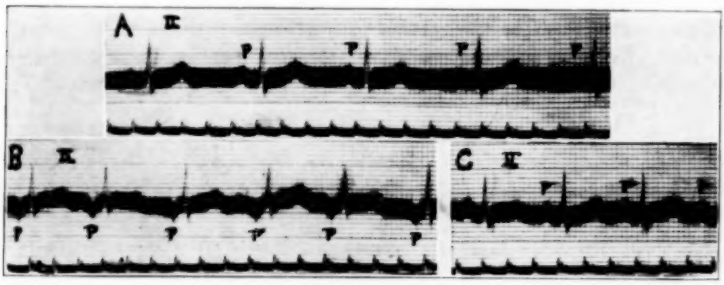

Fig. 5.—Case 17. Operation, tonsillectomy. Lead II. A. Normal tracing, rate 68. P-R interval 0.16 sec. Taken at signal for first incision. B. Inverted P waves, rate 94. P-R interval 0.12 sec. Taken two minutes after A. C. Normal tracing, rate 99. Taken one minute after B.

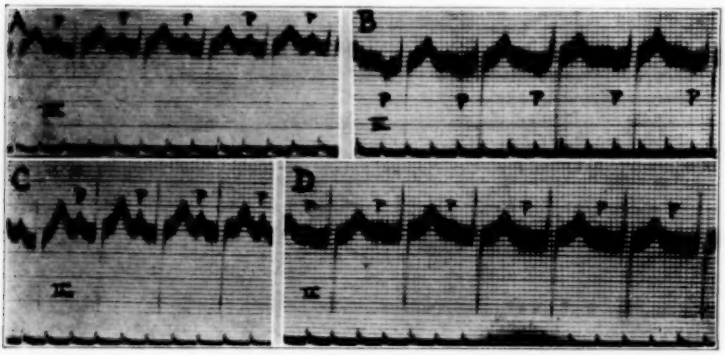

Fig. 6.—Case 21. Operation, avulsion trigeminal ganglion. A. Lead III, normal tracing, rate 121. P-R interval 0.16 sec. B. Lead III inverted P waves, P-R interval 0.12-0.16 sec; rate 101. C. Lead II normal tracing; rate 140. D. Lead II P waves greatly flattened; rate 107. Taken two minutes previous to C.

complex, i. e., either an absence of the wave, or an inverted P wave with diminished P-R interval, or even the P wave following the R wave, producing an R-P interval.

5. Wilson, F. N.: Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated with Respiration, Arch. Int. Med. **16**:86 (July) 1915.

Following the classification used by Wilson [6] in reporting his cases of A-V rhythm which resulted from the injection of atropin, these eleven cases are divided into three groups:

1. *Cases in Which the "P" Wave Is Inverted and the P-R Interval Reduced.*—Three of the patients showed this abnormality. In Figure 5, three successive records are shown. The first was taken on the signal denoting the beginning of operation (tonsillectomy), the second, which shows inverted P waves, two minutes later, and the last one minute after the second. The rate of the heart in the middle (abnormal) record is intermediate between the rates of the other two. Figure 6, from another case, is of interest in that it shows in one lead at one time an inverted "P," and in another lead at another time a markedly flattened "P."

2. *Cases in Which the "P" Wave Is Absent.*—Seven of the cases showed a disappearance of the P wave. Examples from three of these are shown in Figures 7, 8 and 9. In Figures 7 and 8 there is in some of the cycles a slight irregularity of the auricular complex, suggesting an interference of two rhythms. In some instances interpretation was difficult because of the artefacts produced by the operative procedures. Figure 8 is of particular interest for its shows the onset of the abnormal rhythm. Here the transition occurs abruptly, without preliminary shortening of the P-R interval, but with slight slowing of the rate. In Figure 9 (C) a condition of auriculoventricular dissociation probably exists, the auricle responding to the sinoauricular node and the ventricle to the auriculoventricular node. In two of the seven cases, in addition to records showing absent P waves, there are other records showing inverted P waves.

3. *Cases in Which the "P" Wave Is Inverted and There Is an R-P Interval.*—One case belonged to this group. Figure 10 (B) shows the established abnormal rhythm with the heart responding to but one pacemaker. Figure 11 from the same case shows the onset of abnormal rhythm, the P-R interval becoming shorter and shorter until the P wave is lost in the R wave. In this tracing, as in Figure 9 (C), there is a mixed rhythm, the heart responding to two pacemakers. The transition is accompanied by a slight decrease in rate. The operation was the excision of a right cervical rib in a young woman. The operator "neither saw nor touched the vagus nerve."

In addition to the above group of eleven cases, there was one patient whose tracings showed bigeminy and marked differences of the P wave in successive cycles. As his control tracings, both before and after operation, showed the abnormality this case is not included in the

6. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropin, Arch. Int. Med. **16**:994 (Dec.) 1915.

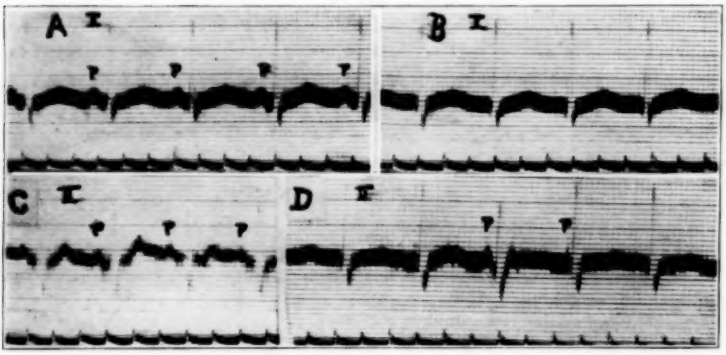

Fig. 7.—Case 25. Operation, excision tumor of cerebrum. A. Lead I, normal tracing; rate 93. B. Lead I, absent P waves; rate 103. C. Lead II, normal tracing; rate 108. Taken seven minutes after beginning of anesthesia. D. Lead II, P waves are in some cycles absent, in others the P-R interval is much diminished; rate 107.

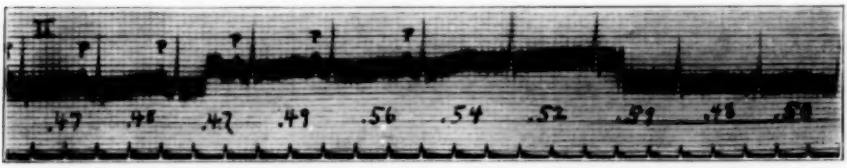

Fig. 8.—Case 31. Operation, cerebellar exploration. Lead II. Note disappearance of P waves with slight decrease in heart rate. Figures indicate length of heart cycles.

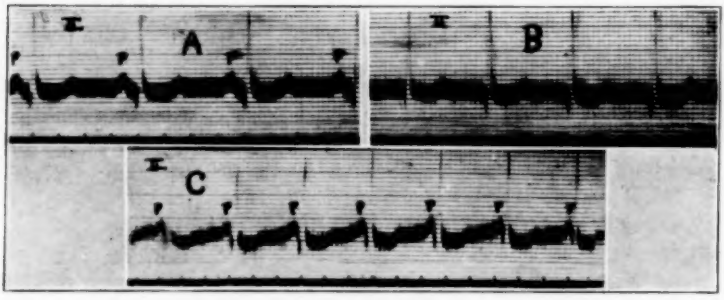

Fig. 9.—Case 1. Operation, suprapubic prostatectomy. Lead II. A. Normal tracing; rate 74. B. Absent P waves; rate 94. Taken three minutes after beginning of anesthesia. C. P-R interval diminished, P upright; rate 110. Taken three minutes after B.

preceding group. One of the eleven cases showed a single record with inverted P waves just before the beginning of anesthesia. Aside from the constantly abnormal case mentioned above, this is the only instance in the series of fifty cases of a disturbance of the pacemaker occurring in any of the control tracings taken before and after operation. In all cases the abnormality had disappeared before the patient left the operating table. Records were taken during convalescence of several

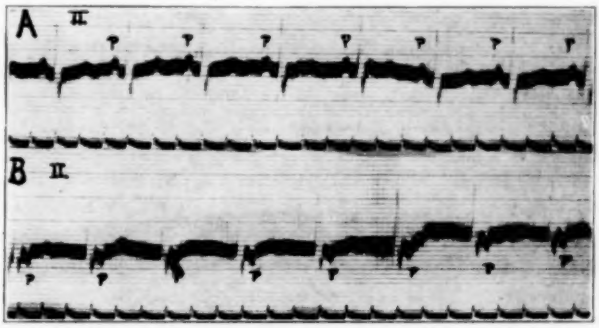

Fig. 10.—Case 22. Operation, excision cervical rib. Lead II. A. Normal tracing; rate 99. Taken at time of first incision. B. Inverted P waves, R-P interval of 0.08 sec.; rate 99. Taken one minute after A.

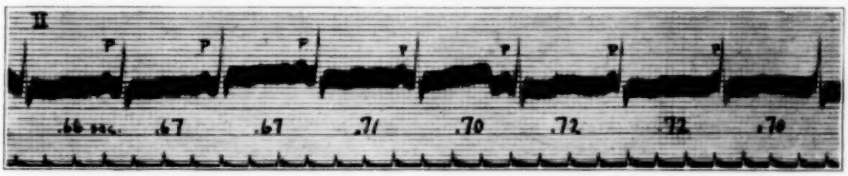

Fig. 11.—Case 22. Lead II. Onset of abnormal rhythm. P is upright, the P-R interval progressively diminishing, with slight decrease in rate. Figures indicate length of heart cycles.

patients who had shown abnormality of P waves during operation. All were found normal. Two of the fifty cases showed auricular waves which were, in some of the tracings, considerably larger than the normal P waves for those individuals.

Significant variations in the height of the R or T waves, other than a transient inversion of a low T wave in one case, were not noted.

DISCUSSION OF CASES SHOWING A MARKED VARIATION IN THE P WAVES

In the preceding section we have sought to present graphic records of abnormalities rather than their interpretation. The question now

arises as to how many of these are examples of A-V (atrioventricular) rhythm. A large proportion of such cases would not be inconsistent with experimental findings. Levine,[7] while taking electrocardiographic records of etherized cats, about every six minutes, found that in fourteen out of forty-seven experiments, tracings showed the presence of A-V rhythm. In almost all instances the abnormal rhythm appeared after the etherization of the animal but before the beginning of the experiment (intravenous injection of strophanthin).

There are difficulties, however, in the way of interpreting all these abnormal tracings in the present study as instances of A-V rhythm. In the first place, there is in the literature a lack of unanimity in the definition of this condition. Should the term be confined to those cases of pure A-V rhythm in which the heart is responding to but one pacemaker located in the A-V node, or should it include cases of mixed or double rhythm in which impulses arise from both the S-A (sino-auricular) and A-V nodes? There is a difference of opinion concerning the criteria by which A-V rhythm is to be diagnosed from electrocardiographic tracings. Some writers consider it essential that the P wave be inverted. On the other hand, the statement appears in a recent paper that in A-V rhythm the P wave is frequently though by no means constantly inverted.[8] Carter and Wedd,[9] in reporting twelve cases of inverted P in Lead III, consider that a transient inversion of P means a displacement of the pacemaker.

Furthermore, in those cases showing P waves, it is a point of issue as to how much shortening of the P-R interval there must be in order to prove that the impulse arises in the A-V node rather than in the auricular tissues adjacent to it. Theoretically, there should be a shortening in the P-R interval of at least 0.03 second, the time consumed by the impulse in passing from the S-A to the A-V nodes.[10] Confusing factors may, however, enter in. Thus, in the presence of vagal stimulation depressing A-V conduction, there may be, coincident with the descent of the pacemaker, a lengthening of the P-R time.[11]

In the tracings in which the P wave does not appear and is buried in the Q R S (ventricular) complex, it is not always clear whether

7. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. M. **29**:493, 1919.

8. Barker, L. F., and Richardson, H. B.: An Unusual Combination of Cardiac Arrhythmia of Atrial Origin Occurring in a Patient with Focal Infection and Thyroid Adenomata, Arch. Int. Med. **23**:158 (Feb.) 1919.

9. Carter, E. P., and Wedd, A. M.: Observations on the Occurrence of inverted and Diphasic P Waves in Lead III of the Human Electrocardiogram, Arch. Int. Med. **23**:16 (Jan.) 1919.

10. Lewis, T.: The Mechanism and Graphic Representation of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 189.

11. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:423 (March) 1920.

the unseen P is upright or inverted. Again, an apparently absent P wave may mean that it has become so greatly flattened in that particular lead as to be isoelectric, though it might appear as a distinct wave in another lead. Another possibility when the auricular complex is absent is standstill of the auricle, described by White.[12]

A further consideration is the lead in which the abnormality appears, for inversion of P in Lead III is not so significant as inversion in Lead II. In tracings made on 700 cases, mostly cardiacs, Goddard[13] found inversion of P in Lead III seventy-five times and in Leads I and II only eleven times. Barker and Richardson,[8] on the other hand, among 400 records found but one showing inverted P waves. In the eleven cases of variation of P waves in this study, all but two showed the abnormality in Lead II.

Because the disturbances in this series were transient and the patients were being operated upon, there was no opportunity for experimentation on the effects of atropin, vagal pressure, etc. We did not have, as did Wilson in his report of A-V rhythm occurring after the injection of atropin, the benefit of simultaneous venous tracings. It would appear certain, however, that all these cases represent various stages of the same process, viz., a dislocation of the pacemaker. (In the cases of auricularventricular dissociation[14] one might more properly speak of a doubling of the pacemakers.) In most of the cases, possibly in all, the pacemaker, or where there are two, one of the pacemakers arises in the A-V node. Because we cannot be certain that all of these are cases of A-V rhythm, we shall designate them simply as the group showing a marked dislocation of the pacemaker.

HEART RATES IN RELATION TO DISLOCATION OF THE PACEMAKER

Dislocation of the pacemaker is explained on the theory either that the rate of the S-A node falls below that of the A-V node, in which case the latter becomes the pacemaker, or that the A-V node is stimulated to a rate above that of the S-A node. In either instance the rates during normal and abnormal rhythm might differ. The heart rates for cases showing dislocation of the pacemaker were charted and found to fall into three classes. Four cases showed a slower rate during the abnormal rhythm. The heart rate of one of

12. White, P. D.: Auricular Standstill, an Unusual Effect of Digitalis on the Heart with Special Reference to the Electrocardiograph, Boston M. & S. J. **175**:233, 1916.

13. Goddard, C. H.: Changes in the P Wave of the Human Electrocardiogram, Arch. Int. Med. **16**:133 (July) 1915.

14. White, P. D.: Ventricular Escape with Observations on Cases Showing Ventricular Rate Greater than that of the Auricles Arch. Int. Med. **18**:244 (Aug.) 1916.

these is illustrated in Figure 12 A. Here after the beginning of operation, whenever the heart rate fell to 125 or below there was an absence of P waves in the electrocardiographic record. In one instance, the heart rate was faster during the period of abnormal rhythm (Fig. 12 B). In six of the cases, the rate bore no relation to rhythm. This group is illustrated (Fig. 13) by the case which showed on R-P interval. As seen in the chart, the rhythm changed on three occasions without a change in rate.

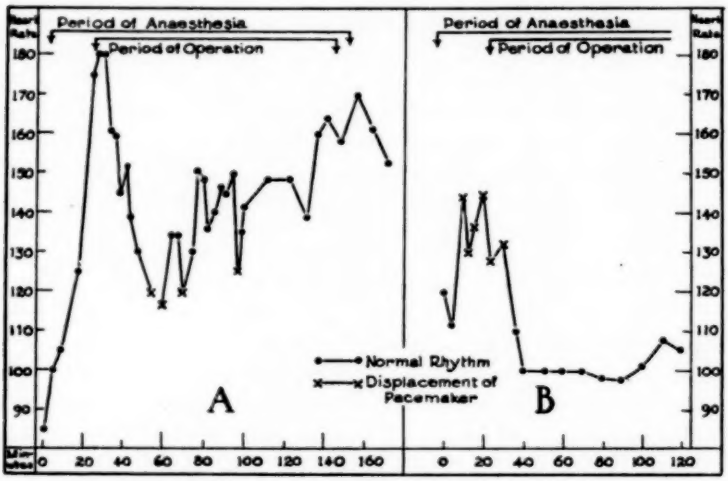

Fig. 12.—A. Note the slower rate which occurs with the displacement of the pacemaker. B. Note the faster heart rate which occurs with the displacement of the pacemaker.

FACTORS IN PRODUCTION OF ABNORMALITIES

In discussing the cause of the abnormalities noted, it is necessary to consider various factors. Twenty-four (48 per cent.) of the cases show some disturbance of the heart beat not present in the preliminary tracings. Eleven of these are classified as showing displacement of the pacemaker (some show other changes as well); thirteen as showing other abnormalities. The number of cases is too small and the factors concerned are too numerous to permit definite conclusions. The following analyses must therefore be regarded simply as interesting observations.

Sex.—Twenty-three of the persons operated on were males, and twenty-five were females. Sex bore no relation to the incidence of abnormality.

Age.—The age of patients varied from 2 to 84 years. Twenty-six were under 40 while twenty-two were over 40 years. The incidence of abnormality for those under 40 was nearly the same as for those over that age.

Cardiovascular Symptoms.—A history of serious infection (scarlet fever, rheumatic fever, chorea, tonsillitis, pneumonia, etc.) was not more common in those yielding abnormal tracings than in the normal group. A history of cardiac symptoms (dyspnea, edema, etc.) was, on the other hand, of some importance. Only 11 per cent. of those with normal tracings gave a story of cardiac disturbances, whereas 41 per cent. of those with abnormal tracings reported such difficulties.

Cardiac Lesions.—Only four of the forty-eight persons showed definite signs of cardiac disease by routine physical examination. Two

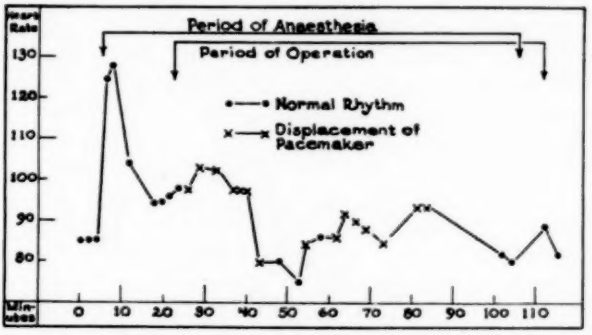

Fig. 13.—Note that a change of rhythm occurs in three instances without a change of rate.

of these (one a case of mitral stenosis and the other of chronic myocarditis) showed abnormal preliminary tracings and the other two (one a case of mitral regurgitation and the other of sclerotic aortic valves) showed some abnormality during operation. In only one case did the condition of the heart cause serious debate as to the advisability of operation. This was a woman with a permanent auricular fibrillation and mitral stenosis who had had repeated attacks of gallstone colic. She was thoroughly digitalized so that on the morning of operation there was no pulse deficit. In order to determine whether a pulse deficit occurred during operation, the anesthetist signaled the times at which she counted the pulse, and simultaneously electrocardiographic records were made. During the period of induction of anesthesia the auricular impulses broke through the digitalis block and the heart rate jumped to 150, while the pulse rate did not exceed 100. In this instance there

was without doubt a real pulse deficit. During the period of actual operation, however, there was no deficit. Cholecystectomy was performed without any difficulty and the patient left the hospital in satisfactory condition.

Blood Pressure.—With due consideration to the age of the patients, five of forty-five patients had high blood pressures, and nine had pressures which seemed to be low. Abnormality of blood pressure in this series bore no relation to abnormality of the heart mechanism.

Position During Operation.—Normal records were obtained more frequently in those patients who were placed flat on the table than in those in other positions. It is probable, however, that other factors were operative in these cases.

Preliminary Medication.—Thirty-seven of the patients received preliminary morphin (usually 0.01 gm.) and atropin (0.0005 gm.). Seven received morphin only and six had no preliminary medication. Wilson [6] has shown that for from eight to fifteen minutes following the injection of 1 mg. atropin, vagal stimulation produced an A-V rhythm in the majority of his twenty cases. The abnormal rhythm could not be produced after twenty minutes had elapsed. In this series the atropin would not be expected to cause A-V rhythm, for the dose was only one half that used by Wilson and at least thirty minutes intervened before the beginning of the observations. Of the thirty-seven cases receiving atropin, six (16 per cent.) showed a disturbance of the pacemaker; of the thirteen cases not receiving atropin, five (38 per cent.) showed this change. The preliminary atropin would seem to diminish rather than increase the chances of inducing the abnormal rhythm. Concerning morphin, Cohn [15] has shown in dogs that the action of the drug is similar to vagus stimulation. In our forty-four cases receiving morphin, however, eight patients had disturbances of the pacemaker, while of the six not receiving it, three showed these changes. The observations are too few to warrant any conclusions as to the role that morphin may play in the production of abnormalities.

Lack of Oxygen.—The work of Greene and Gilbert [16] suggests that anoxemia may be a factor in producing A-V rhythm; for, of their twenty-one soldiers who breathed air having a low oxygen tension, six showed this disturbance. In none of our cases was there any apparent lack of oxygen, although the routine anesthetization in the operating room did not provide any accurate data on this point.

Type of Anesthesia.—All of the anesthesias were given by one of a staff of three trained anesthetists. Twenty of the patients received

15. Cohn, A. E.: The Effect of Morphin on the Mechanism of the Dog's Heart After Removal of One Vague Nerve, J. Exper. M. **18**:715, 1913.

16. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tensions, Arch. Int. Med. **27**:517 (April) 1921.

ether, thirteen by the open drop method and seven through an intrapharyngeal tube, using the Connell apparatus. Twenty-two had nitrous oxid and oxygen, and eight had local anesthesia (procain). The abnormal rhythm occurred in seven (35 per cent.) of the cases receiving ether, in three (14 per cent.) of those receiving gas-oxygen and in one (12 per cent.) of those who had procain. It was present in but 15 per cent. of the cases in which ether was given by the drop method but occurred in 70 per cent. (five out of seven) of the cases in which ether was given by means of a nasal tube introduced into the pharynx. Considering all forms of disturbances of the heart mechanism, abnormalities were not more common with one kind of anesthesia than with another.

Length of Anesthesia and Operation.—The longest period of anesthesia was three hours and five minutes and the shortest twenty-two minutes, the average being eighty-five minutes. Abnormalities were more frequent in the longer procedures than in the shorter ones.

Type of Operation.—The distribution of operative fields was as follows: head, six; throat and neck, seven; chest, one; intra-abdominal, nineteen; extraperitoneal, eleven; extremities, six. The chief differences were noted between operations involving the head and neck and those on other parts of the body. Of the former, 70 per cent. showed some type of abnormality in the electrocardiograph record, while of the latter 40 per cent. were abnormal. The fact that head operations were longer than those of other types does not account for this greater incidence of abnormalities, because abnormalities occurred in almost every case during the early part of the operation. A disturbance of the pacemaker was present in 46 per cent. of the thirteen operations involving the region above the clavicles, and in only 13 per cent. of all other operations. In several instances abnormality seemed to follow critical steps in the operative procedure, but in the great majority of cases no such relationship was evident.

Frequency of Records.—In five of the eleven cases of disturbance of the pacemaker, the abnormality appeared in one or two records only. It is possible, therefore, that other cases presented abnormalities of which records were not obtained. For all those cases showing abnormality, the interval of time between records is the same as for those showing no abnormality.

Time of Occurrence.—Figure 4 presents the time relations for cases showing premature beats (upper part) and disturbances of the pacemaker (lower part). In every instance except one the abnormal rhythm appeared during either the induction of anesthesia or the first third of the operation. This points to factors other than fatigue as a cause of this abnormality.

In reviewing the evidence in this study it seems that the incidence of a displacement of the pacemaker is greater in patients having head and neck operation, intrapharyngeal anesthesia, or when preliminary atropin is omitted. It is possible that vagal stimulation is in some way concerned in these procedures. The production of premature beats does not seem to be clearly related to any of the factors considered. None of the cases showing abnormal electrocardiograms gave clinical evidence during operation of an embarrassed circulation. Though abnormality in the mechanism of the heart beat occurred with surprising frequency, these periods were transient and of physiological rather than clinical significance.[17]

SUMMARY

An electrocardiographic study of fifty cases was made during anesthesia and surgical operation.

1. In many cases the electrocardiographic tracings revealed a heart rate considerably faster than the pulse rate recorded by the anesthetist.

2. About one half of the cases showed some abnormality of the mechanism of the heart beat, not present in preliminary tracings, the most prominent being: paroxysmal auricular tachycardia; premature beats, and marked displacement of the cardiac pacemaker.

3. Various factors which might contribute to the production of the abnormalities named are analyzed. Only those which might possibly be concerned with alterations in vagal tone, seem to be of importance.

4. The observed abnormalities of the heart beat were transient and unassociated with clinical signs of embarrassed circulation. In the main, they were of physiological rather than of clinical significance.

We wish to thank Dr. Harvey Cushing and his associates, as well as the staff of the operating room, for their generous cooperation in this study.

17. A table giving detail of cases appears in authors' reprints.

STUDIES ON THE PHYSIOLOGY OF THE LIVER

II. THE EFFECT OF THE REMOVAL OF THE LIVER ON THE BLOOD SUGAR LEVEL *

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ROCHESTER, MINN.

In previous articles,[1] a method was described for the total removal of the liver from the dog, and a brief summary was made of the data obtained from a series of studies on the completely hepatectomized animal. The present report deals more in detail with one phase of our experiments; namely, the effect of hepatectomy on the sugar concentration of the blood.

Method for Total Removal of the Liver of the Dog.—Since the method of removal of the liver has been fully described,[1] only a brief description will be given. The liver is removed in two stages. All operations are performed under ether anesthesia with aseptic surgical technic.

The first operation consists of a reverse Eck fistula, that is, lateral anastomosis of the portal vein and the vena cava and ligation of the latter on the cephalic side of the stoma. At first a considerable portion of the blood from the posterior portion of the body passes through the liver, but since the capillaries of the liver offer more resistance to the flow of blood than is necessary for the development of collateral circulation through the azygos and internal mammary veins, most of the blood soon passes by way of the latter channels.

The second operation consists in the ligation of the portal vein at its entrance into the liver. This causes all the blood from the viscera and hind legs to return by way of the collateral vessels, the azygos, and the internal mammary veins. If, as sometimes occurs, collateral vessels fail to develop sufficiently, as is recognized by congestion of the intestines after ligation of the portal vein, the occlusion of the portal vein is carried out in two stages. In such case the ligature is removed from the vein which is partially occluded by passing

* From the Division of Experimental Surgery and Pathology, The Mayo Foundation, and the Section on Clinical Laboratories, Mayo Clinic.

1. Mann, F. C.: Studies in the Physiology of the Liver. I. Technic and General Effects of Removal, Am. J. M. Sc. **161**:37, 1921. Also: Am. J. Physiol. **55**:285, 1921.

Mann, F. C., and Magath, T. B.: II. The Liver as a Regulator of the Glucose Concentration of the Blood, Am. J. Physiol. **55**:285, 1921. III. The Nitrogen Constituents of the Blood Following Removal of the Liver, Am. J. Physiol. **55**:286, 1921.

Mann, F. C., and Magath, T. B.: The Effect of Total Removal of the Liver, Tr. Sect. Path. & Physiol. A. M. A., 1921, p. 29.

a blood vessel suture through the center and ligating one side. At a later operation the portal circulation is entirely occluded. The third operation consists of removing the entire liver. This is accomplished without disturbing the general circulation.

Symptoms Following Total Removal of the Liver of the Dog.—The clinical course of events is very definite and varies but slightly in different animals. Recovery from anesthesia and from the immediate effects of the operation is rapid. One hour after operation, the animal usually appears almost normal,[2] and remains so from three to eight hours. During this period the animal is to all appearances normal; it walks around, responds to call, exhibits the usual interest in other dogs, and drinks water.

The onset of the moribund period is usually sudden and the subsequent development of various symptoms typical and rapid. The first symptom noted is muscular weakness. The animal cannot hold itself erect, or avoid swaying when walking, and prefers to lie down. The muscular weakness develops quickly and in a short time the animal is unable to move any of its muscles, except those necessary for respiration. Coincident with this development of muscular weakness is a decrease and subsequent loss of reflexes. Usually, within an hour after evidence of muscular weakness is first noted, the animal lies quietly breathing, with muscles flaccid and relaxed. This period of flaccidity may be short, but in a few animals it has lasted for several hours. After a variable period, usually not more than one hour, there is a rather sudden return and exaggeration of the reflexes. Muscular twitchings develop, at first involving separate muscles or small groups of muscles, then general convulsions occur in one of which the animal dies. In typical experiments the animal vomits a few seconds before death.

The symptoms and the order of their occurrence are: muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitchings, and convulsions. The development of these symptoms is extraordinarily constant. The average animal, if untreated after hepatectomy, dies within two hours after the appearance of the first signs of muscular weakness.

The blood pressure seems to be practically normal while the animal is active. When the first symptom develops, the blood pressure decreases but does not necessarily fall to a low level. The pulse usually becomes practically twice as rapid as normal. Just before death the rate may become slower than normal. The heart continues to beat

2. In order to express the difference between the hepatectomized animal when not showing symptoms and at the stage just preceding death, "normal" and "moribund" have been employed. "Normal" means that the animal appears to be normal; "moribund," that the animal appears to be dying.

for a long time after breathing has ceased. The respiration undergoes certain changes following operation, varying with the condition of the animal. Often the animal is in coma, and Cheyne-Stokes type of respiration is noted. The temperature usually continues normal until the animal becomes flaccid, although just previous to the development of muscular weakness, it may rise one degree higher than it was before operation. It may become subnormal before death. Some of the

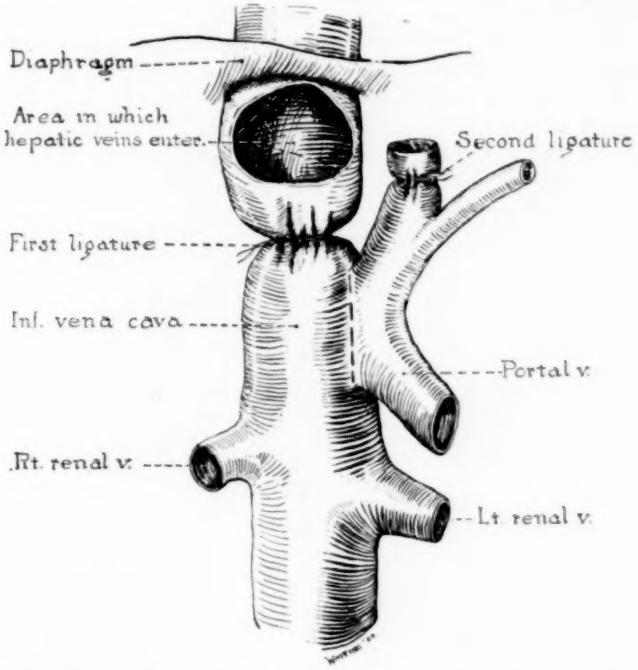

Fig. 1.—Diagram illustrating the steps in the technic of the removal of the liver. At the first operation the portal vein and vena cava are anastomosed along the dotted line and the first ligature is placed. At the second operation, after the collateral circulation has been established, the second ligature is placed. At the third operation the liver and the portion of the vena cava between the ligature and diaphragm are removed.

animals secrete practically a normal amount of urine before they develop symptoms, but others are anuric throughout the postoperative period.

Previous Observations on the Symptoms Occurring After Removal of the Liver.—Some of the symptoms noted after exclusion or removal of the liver have been observed by previous investigators who particu-

larly noted the convulsions and coma. Minowski [3] observed these symptoms in some of his geese after extirpation of the liver. Kausch [4] particularly emphasized the occurrence of convulsions in his study of hepatectomized geese. Hahn, Maassen, Nencki and Pawlow [5] noted muscular twitchings, convulsions, and coma in dogs in which Eck fistulas had been made and the hepatic artery ligated. Doyon, Gautier and Policard [6] record the development of typical convulsions in frogs following removal of the liver. Whipple and Hooper [7] observed muscular twitchings in dogs with Eck fistulas and ligation of the hepatic artery. Matthews and Miller [8] report that animals in which the hepatic artery was ligated some weeks after the making of an Eck fistula became comatose from eight to twelve hours after the ligation.

The study most comparable to ours was made by Perroncito,[9] who removed the liver with little disturbance of the circulation, and the animals developed the characteristic symptoms of hepatic insufficiency. His description of the symptoms corresponds quite closely to our own.

The failure of previous investigators to observe the production of a definite group of symptoms may be owing to several causes. In most investigations the experiments were performed in order to obtain definite data with regard to a particular fact concerning the liver; practically all the experiments were complicated by marked derangement of the circulation or by an anesthetic or narcotic so that symptoms could not be observed.

In a large number of studies on hepatectomized animals the most pronounced and constant phenomenon which attracted our attention was a progressive, invariable decrease in the sugar content of the blood.

Previous Work on the Effect on Blood Sugar of Removal of the Liver.—The first experiments on the effect of exclusion of the liver

3. Minkowski, O.: Beiträge zur Pathologie der Leber auf den Stoffwechsel. III. Ueber den Einfluss der Leberexstirpation auf den Stoffwechsel, Arch. f. exper. Path. u. Pharmakol. **21**:41, 1886.

4. Kausch, W.: Der Zuckerverbrauch im Diabetes Mellitus des Vogels nach Pankreasexstirpation, Arch. f. exper. Path. u. Pharmakol. **39**:219, 1897.

5. Hahn, M.; Massen, O.; Nencki, M., and Pawlow, J.: Die Eck'she Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen für den Organismus. Arch. f. exper. Path. u. Pharmakol. **32**:161, 1893.

6. Doyon, M.; Gautier, C., and Policard, A.: Lésions rénales déterminées chez la grenouille par l'ablation du foie. Rappél aux textes. Compt. rend. Soc. de biol. **64**:271, 1908.

7. Whipple, G. H., and Hooper, C. W.: Icterus. A Rapid Change of Hemo-Globulin to Bile Pigment in the Circulation Outside the Liver, J. Exper. M. **17**: 612, 1913.

8. Matthews, S. A., and Miller, E. M.: A Study of the Effect of Changes in the Circulation of the Liver on Nitrogen Metabolism, J. Biol. Chem. **15**:87, 1913.

9. Perroncito, A.: Sulla estirpazione del fegato, Riforma med. **36**:830, 1920.

on blood sugar seem to have been made by Bock and Hoffman.[10] They excluded the liver from rabbits by ligating the abdominal aorta, portal vein, and inferior vena cava between the entrance of the renal and the hepatic veins. Specimens of blood were obtained from the heart by passing an obturator through the inferior vena cava. Animals thus operated on lived from two to fifty minutes. The blood sugar decreased, and no sugar could be found in the blood of animals living as long as forty-four minutes. These experiments have been severely criticized by subsequent workers because the circulation is so greatly damaged by the procedure.

Minowski,[3] in his classical research on the effect of removal of the liver in geese, noted a decrease in blood sugar. Seegen [11] excluded the liver in dogs by ligation of the aorta and vena cava above the

Fig. 2.—Side of the abdominal wall of animal showing the dilated veins of the skin which follow the operative procedures necessary to prepare the animal for total removal of the liver. In many animals these veins do not dilate but the entire collateral circulation is developed through the great azygos vein.

diaphragm. The animals lived from twenty to seventy minutes. A marked reduction in the blood sugar was observed. Schenck [12] ligated the base of the liver, probably obstructing both the portal vein and the vena cava. A decrease in blood sugar was noted. Kaufmann [13] repeated

10. Bock, C., and Hoffman, F. A.: Experimental Studien über Diabetes. Berlin, H. E. Oliven, 1874.

11. Seegen, J.: Die Zuckerbildung im Thierkärper, ihr Umfang und ihre Bedeutung, Berlin, A. Hirschwald, 1890.

12. Schenck, F.: Ueber den Zuckergehalt des Blutes nach Blutentziehung, Arch. f. d. ges. Physiol. **57**:553, 1894.

13. Kaufmann, M.: Nouvelles recherches sur la pathogénie du diabéte pancréatique. Compt. rend. Acad. d. Sc. **118**:656, 1894; De l'nfluence exercée par la suppression partielle ou totale de la fonction hépatique sur la glycémie chez les animaux normaux et diabétiques, Arch. de physiol. norm. et path. **8**:151, 1896.

Seegen's experiments; that is, he ligated the aorta and inferior vena cava above the diaphragm in dogs and observed a rapid diminution of sugar in the blood. His animals lived for about one hour. Kausch [4] repeated Minkowski's work on geese and corroborated the latter's findings with regard to a decrease in blood sugar after removal of the liver. Macleod and Pearce [14] restricted the circulation in dogs to the anterior portion of the body and obtained a rapid reduction in blood sugar.

Pavy and Siau [15] performed experiments on cats and dogs. In the former, all the viscera were removed except the liver; in the latter the liver and the other organs also were removed. The blood sugar progressively dropped, but was never wholly depleted.

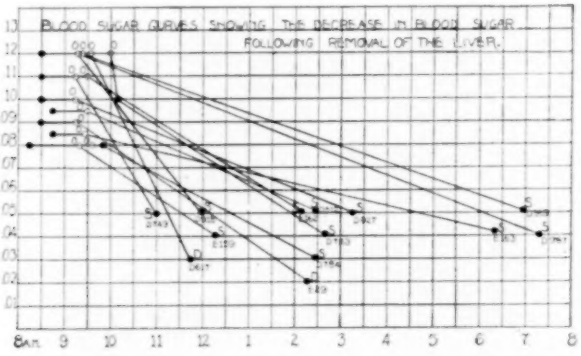

Fig. 3.—The blood sugar was estimated before operation. O: Liver removed. S: Animal moribund. D: Blood of two animals taken at the time of death. All the animals were kept as nearly as possible, under the same conditions. Note the marked decrease and the rather constant level at which the animals became moribund. The average curves of blood sugar were taken from this group.

Investigations of the effect of the removal or exclusion of the liver on blood sugar, therefore, show that a reduction of blood sugar was obtained in each instance. Most investigators have attributed little significance to this fact. The liver was not surgically removed from any of the animals except the goose. The different methods of exclusion entailed a very great alteration in the circulation and, except in those experiments in which the circulation was restricted to the anterior part of the body, a great loss of blood must have occurred from congestion.

14. Macleod, J. J. R., and Pearce, R. G.: The Sugar Consumption in Normal and Diabetic (depancreated) Dogs After Evisceration, Am. J. Physiol. **32**: 184, 1913.

15. Pavy, F. W., and Siau, R. L.: The Influence of Ablation of the Liver on the Sugar Contents of the Blood, J. Physiol. **29**:375, 1903.

The method of experimentation and length of life after operation, with the exception of experiments with geese, precluded any correlation between the reduction of blood sugar and the development of symptoms.

Methods of Blood Sugar Estimation.—A specimen of blood for estimation of blood sugar was obtained from the jugular vein before operation. The liver was removed under ether anesthesia and sterile technic. In most experiments another specimen of blood for the estimation of blood sugar was taken immediately after operation and then at hourly intervals until the animal was moribund. In a few experiments only two blood sugar estimations were made, one just before operation and the other when the animal became moribund.

The blood sugar concentration was estimated by the Benedict [16] modification of the Lewis-Benedict method. Our collaborators, who made most of the estimations, had had an enormous experience with this method in the clinical laboratory, the records of which could be used as controls of our estimations. Moreover, it was early foreseen that it would be necessary to make a very large number of blood sugar estimations, and this method was preferred for quantity work. After the investigation was well under way, parallel estimations were run by two other methods, that of Folin and Wu [17] and Maclean's [18] modification of Bang's method, each of which was very difficult to employ in estimating low concentrations of blood sugar. Hitherto, most studies in blood sugar have dealt with normal or high values; our investigation dealt mainly with subnormal and very low values. For these reasons the Benedict modification of the Lewis-Benedict method was most satisfactory.

It is recognized that there may be substances other than glucose in the blood capable of reducing picric acid or copper sulphate. It is possible that in our determinations the results have included some of these substances. However, this in no wise invalidates our general results for in each instance the same condition resulted in the same rises and falls and, as will be shown, the evidence is overwhelming in substantiating the statement that glucose only was being determined.

All the work has been controlled carefully. The operative work and the taking of blood specimens was done in one laboratory by one group of workers and blood sugar estimations were made in another laboratory by another group of workers. The specimens of blood were immediately marked with the animal's number and the specimen number

16. Benedict, S. R.: A Modification of the Lewis-Benedict Method for the Determination of Sugar in the Blood, J. Biol. Chem. **34**:203, 1918.

17. Folin, O., and Wu, H.: A System of Blood Analysis. Supplement I. A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

18. Maclean, H., and de Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. M. **14**:103, 1921.

and sent to the laboratory. The worker who made the blood sugar estimations had no knowledge of the character of the experiment. At the conclusion of the experiment the data from the two laboratories were correlated, thus completing the experiment.

In a few experiments estimations of the glycogen content of the muscles were made before and after removal of the liver; the method employed for the separation and estimation of the glycogen was that described by Pflüger.[19]

The Effect of Environmental Factors on the Blood Sugar.—The effect of the operative procedure for obtaining the specimen for blood sugar estimation has been repeatedly emphasized as a complicating factor in all experimental data on blood sugar.[20] It is undoubtedly

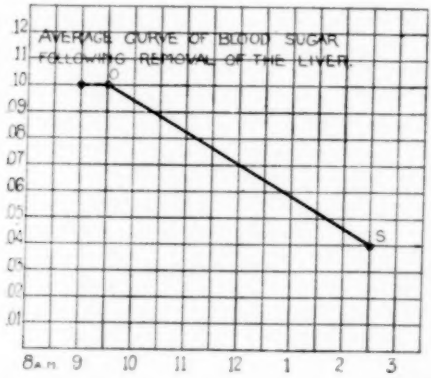

Fig. 4.—The average change in blood sugar noted in thirteen dogs following removal of the liver. O: Point at which the liver was removed. S: Point at which the animal became moribund.

true that such a procedure, or any procedure which may excite or frighten an animal, may cause a change in blood sugar. In our experience of several thousand blood sugar estimations on dogs, such a

19. Pflüger, E.: Meine Methode der quantitativen Analyse des Glykogens und die Arteigenthümlichkeit der Substanzen des Thierleibes, Arch. f. d. ges. Physiol. **129**:362, 1909.

20. Pavy, F. W.: An Enquiry Into the Effects on the Blood and Urine of the Intravenous and Subcutaneous Injection of Various Carbohydrates Standing in Relation to Animal Life, J. Physiol. **24**:479, 1899.

Scott, E. L.: The Content of Sugar in Blood Under Common Laboratory Conditions, Am. J. Physiol. **34**:271, 1914.

Shaffer, P. A.: On the Normal Level of Blood Sugar of the Dog, J. Biol. Chem. **19**:297, 1914.

Boehm, R., and Hoffmann, F. A.: Beiträge zur Kenntniss des Kohlenhydratstoffwechsels. Arch. f. exper. Path. u. Pharmakol. **8**:271, 1878.

Cannon, W. B.: The Emergency Function of the Adrenal Medulla in Pain and the Major Emotions, Am. J. Physiol. **33**:356, 1914.

complicating factor is of very slight significance in most experiments. Our observations show that if blood sugar estimations made every quarter or half hour, for a period of four to six hours, are plotted against the time, the resulting graph is practically a straight line. The effect of environmental factors could only be of importance in experiments in which very slight changes of a hyperglycemic character were being observed. In the series of experiments reported in this paper, this factor was negligible because we were studying hypoglycemia.

The Results on the Blood Sugar Level of Total Hepatectomy in the Dog.—In our experiments a decrease in blood sugar has always occurred after the total removal of the liver. Of greater interest, however, is the fact that the amount of blood sugar exactly paralleled

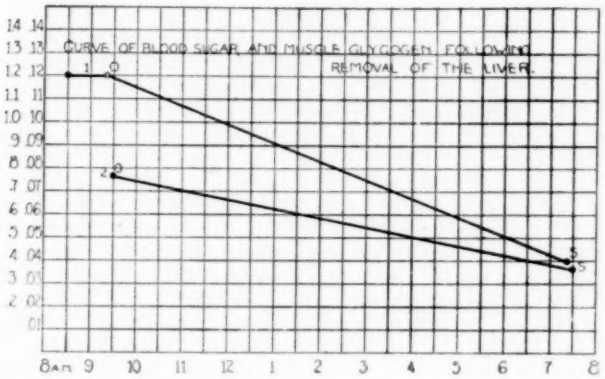

Fig. 5.—O: Liver removed. S: Symptoms developed. First curve shows decrease in blood sugar following removal of the liver. Second curve shows parallel decrease in the muscle glycogen following removal of the liver.

the clinical condition. The blood sugar in our animals before removal of the liver was usually slightly lower than the average for normal dogs. This is to be attributed to the fact that the portal blood supply of the liver had been deflected, as the average blood sugar of dogs with true Eck fistulas has also been slightly below the average for normal dogs. The anesthesia and operative procedure of hepatectomy did not cause the hyperglycemia which is usually noted after anesthesia and operative procedure on normal dogs. The blood sugar concentration immediately after hepatectomy was the same or less than that preceding operation, and very rarely 0.01 per cent. higher; it decreased during the period the animal appeared normal. The level of blood sugar at which the first symptoms developed was usually quite definite and coördinate in the different animals. In most of the dogs this was 0.05 per cent.

In some instances the first symptoms were noted when the blood sugar was 0.06 per cent. and often when it was 0.04 per cent. The blood sugar decreased quite rapidly after the onset of convulsions and at the time of death was usually not in excess of 0.03 per cent. This direct relationship of blood sugar and the development of symptoms and death was so constant that the blood sugar could be estimated correctly after an examination of the animal's clinical condition when it showed symptoms.

The Effect of Hepatectomy on the Glycogen Content of the Muscles.—In one carefully performed experiment a specimen of muscle was

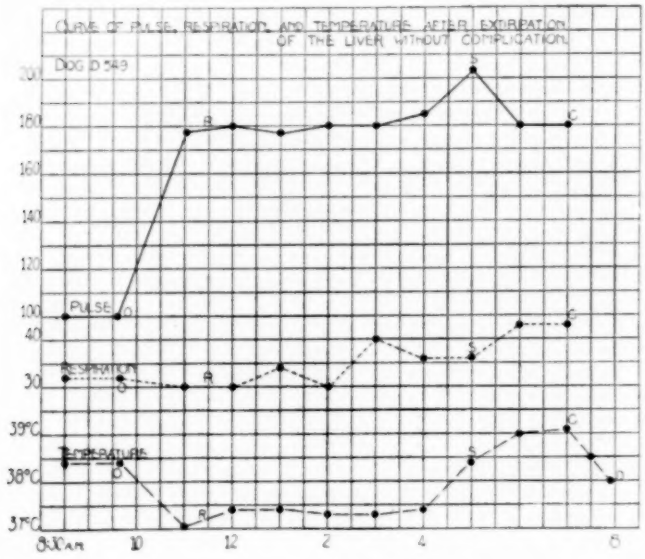

Fig. 6.—O: Liver removed. R: Animal appeared normal. S: First evidence of muscular weakness. C: Convulsions. D: Animal died.

excised at the same time the liver was removed. When the animal became moribund, another specimen of muscle was taken. An estimation of the glycogen content of these two specimens of muscle revealed that the glycogen had decreased about 50 per cent.

The Effect on Blood Sugar of Removal of the Liver of the Goose, Frog, Fish, and Turtle.—In all of these species the portal vein may drain into the general venous system without passing through the liver, and the liver is not so intimately related to the vena cava as it is in mammals. It is thus possible to remove the entire liver without obstructing the portal or vena cava circulation.

We have corroborated the findings of Minkowski and Kausch who obtained a reduction in blood sugar by removal of the liver from the goose. The effects of extirpation of the liver in the goose differ slightly from those obtained in the dog. The symptoms are not so marked and the blood sugar does not fall so low. The length of life after operation varied from eight to twenty hours. The main symptoms were muscular twitchings and convulsions.

The liver of the frog has been removed by other investigators. This species was of no value in our problem because the level of blood sugar in the normal animal is so low. In all the specimens of frog's blood examined the normal value was from 0.03 to 0.04 per cent. These observations were made on fasting frogs in captivity and the blood sugar might have been higher than this immediately after the animal was captured. The length of life after operation varied greatly in this species. Some frogs died within eight hours after hepatectomy, although one lived eight days. A frog might live normally for several days after total removal of the liver and then become flaccid and die within half an hour after the appearance of symptoms. They did not develop marked symptoms. At death the blood sugar was too low to estimate.

The fishes studied (gar pike and dogfish) had a high blood sugar; removal of the liver caused a marked decrease. The effect on the turtle, which normally also has a relatively high blood sugar value, was the same as on the fishes, namely a marked decrease of blood sugar.[21]

DISCUSSION

Our data prove conclusively that: (1) the total removal of the liver is always followed immediately by progressive decrease in the sugar content of the blood, and (2) the development of the characteristic symptoms, which quickly led to death, exactly paralleled this decreasing blood sugar level. Certain symptoms appeared when a definite blood sugar value was reached, others occurred when the level had decreased, and death occurred at a fairly constant point in relation to blood sugar. These facts may be explained variously, but there are two main possibilities. The symptoms and death and the decreasing blood sugar may be dependent on some third unknown factor or factors, or, as is probably true, the blood sugar and symptoms may bear a relationship of cause and effect. Concerning the first possibility we have no data and at present it must remain as a mere possibility. It seems to us that the exact relationship between the blood sugar level and the development of symptoms and death following hepatectomy is based on cause and effect. The removal of the liver causes a decrease

21. These two species will be discussed in a separate paper.

in blood sugar and when a certain point is reached, characteristic symptoms develop; when a lower level is reached death occurs.

Why the blood sugar disappears after hepatectomy is another problem with two main possible explanations. Removal of the liver may allow some toxic substance in the blood to develop and combine, chemically or physically, with the glucose and this may be responsible for the symptoms and death of the animal. The truth of this is not supported by any evidence. A more plausible explanation of the cause of the decrease in blood sugar is that hepatectomy removes either the control of the sugar supply or sugar utilization, and the symptoms and death are actually due to a lack of glucose as food. Removal of the liver may produce a depletion in the carbohydrate material of the body either directly by removal of the store of carbohydrates and the place of its elaboration, or indirectly by removal of a substance which has to do with carbohydrate utilization. The latter possibility might be brought about in one of two ways: (1) either directly by controlling the rate of glucose metabolism, or (2) indirectly by controlling the rate of protein or fat metabolism.

SUMMARY

There is a marked and progressive decrease in the blood sugar following total removal of the liver. The glycogen content of the muscles also decreases. Coincident with this decrease in blood sugar, a characteristic group of symptoms develop and progress until death occurs. This effect of hepatectomy on blood sugar has been observed in markedly different species; namely, dog, goose, turtle, and fish. In each species investigated, removal of the liver produced a marked decrease in blood sugar. The relationship of the decrease in blood sugar and the development of the characteristic symptoms seems to be one of cause and effect.

THE ELIMINATION OF ARSENIC IN THE URINE OF SYPHILITIC PATIENTS AFTER INTRAVENOUS INJECTION OF ARSPHENAMIN *

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PHILADELPHIA

Although the literature on arsphenamin has become extremely voluminous, yet there are relatively few reports of work done on the important subject of arsenic elimination after intravenous injection of this drug in which the arsenic determinations have been made by modern, accurate methods. Moreover, the older literature from 1910 to 1913 deals mostly with the intramuscular and subcutaneous methods of administration which are no longer in vogue today. For this reason, it has been deemed advisable to reinvestigate this subject on a series of carefully controlled patients with the use of more recent and acceptable methods.

REVIEW OF THE LITERATURE

The literature up to 1913 has been thoroughly reviewed by Ullman.[1] We have gone over this literature and after thorough analysis, have decided to omit from this discussion the work of those authors [2] who used inadequate methods for the destruction of the organic matter of the urine or tissues or for the quantitative determination of arsenic.

Frenkel-Heiden and E. Navassart [3] in 1913 published carefully obtained data on arsenic elimination after intravenous injections of arsphenamin. They used the sulphuric and nitric acid method for destroying organic matter and the Marsh mirror method for estimating arsenic as metallic arsenic. After a dose of 0.6 gm. they detected in the urine during the first three days after injection 5.10, 1.40 and 0.08 mg., respectively, of arsenic. This gives 6.58 per cent. elimination in three days. During the next ten days small amounts, 0.15, 0.80, 0.10, etc., to 0.07 mg. were detected. In another patient with the same dose (0.6 gm.) only 1.6 per cent. was eliminated in the first

* From the Dermatological Research Institute, Philadelphia. (Investigations aided by funds accruing from the preparation of arsphenamin.)

1. Ullmann, K.: Elimination and Storage of Salvarsan After Injection Into the Human and Animal Body, Arch. f. Dermat. u. Syph. **13**:114, 511, 1912.

2. Abelin, J.: Beginning and Duration of Elimination of Salvarsan in the Urine After Injection, Ehrlich's Abhandlungen über Salvarsan **2**:45, 1911. Greven, K.: The Beginning and Duration of Elimination of Arsenic in the Urine After Treatment with Salvarsan, Ehrlich's Abhandlungen über Salvarsan **1**:56-58, 1911.

3. Frenkel-Heiden and Navassart, E.: Ueber das Schicksal des Salvarsans im menschlichen Körper, Ztschr. f. Exper. Path. u. Therap. **13**:531, 1913.

three days and somewhat larger quantities were eliminated during the succeeding ten days. The figures beginning with the first day are 1.8, 0.8, 0.2, 0.6, 0.2, 0.4, 0.1 mg. arsenic, etc.—down to unweighable traces from the seventeenth to the twentieth day. With smaller doses (0.4 gm.) their figures were similar: 5.6, 0.5, 1.1, 0.4, 0.1 mg., etc.—to 0.07 mg. in one case and 0.5, 0.3, 0.7, 0.5, etc., to 0.1 mg. in another case. In the latter case the feces showed on the corresponding days 4.6, 10.3, 7.3, 2.1, 1.0, 0.8, 0.9 and 0.5 mg. arsenic, respectively. The amount of arsenic eliminated in the feces was therefore almost eight times as great as that in the urine.

Ullman,[1] who made many valuable contributions to the toxicology of arsphenamin, published a limited number of daily analyses on the urine and feces of patients receiving intravenous injections of arsphenamim. He used the hydrochloric acid potassium chlorate method for destroying organic matter and determined arsenic by the Marsh mirror method after converting it into a sulphide. His own check analyses indicate that 26 per cent of the arsenic was lost in the process of destruction of organic matter. In the urine of the first of his series of patients who received 0.4 gm. arsphenamin intravenously, he detected during the first three days 3.9, 3.1 and 1.4 mg. arsenic, respectively. This is equivalent to a total of 7 per cent. of the amount of arsenic administered. With doses of 0.3 gm. arsphenamin he found in one patient 4.6, 2.2 and 1.6 mg. arsenic, respectively, during the first three days, and in another patient 8.2, 2.7, 0.3, 0.8 and 0.1 mg., respectively, during the first five days. The percentages of elimination during the first three days were 9.3 and 12.2 per cent., respectively.

The work of Willcox and Webster,[4] although very important from a toxicologic standpoint, unfortunately does not include daily analyses of the urines. For this reason it is difficult to make comparisons. We may say, nevertheless, that, in general, the quantities detected by them are not much different from ours. In a study of the feces of one case they determined daily eliminations of 1.06, 1.90 and 1.29 mg. arsenic, respectively, making a total of 4.25 mg. arsenic during the first three days following intravenous injection of a 0.6 gm. dose of arsphenamin.

Almost simultaneously, Lockemann[5] published extensive analyses, using an improvement of the Marsh mirror method. After an intravenous injection of 0.38 gm. arsphenamin (114 mg. arsenic) the amounts eliminated during the first thirteen days were 1.86, 0.36, 0.27,

4. Wilcox, W. H., and Webster, J.: The Toxicology of Salvarsan, Brit. M. J. **1**:473, 1916. Webster, J.: The Analyst **41**:231, 1916.

5. Lockemann, J.: Vergleichende Untersuchungen über die Arsenausscheidung durch den menschlichen Harn nach Injektion verschiedener Arsenikalien, Biochem. Ztschr. **78**:1, 1916.

0.29, 0.18, 0.03, 0.11, 0.07, 0.03, 0.05, 0.09, 0.02 and 0.04 mg., arsenic, respectively. This represents a total elimination of 2.98 per cent. arsenic or 2.1 per cent. during the first three days. Eight other cases injected with either arsphenamin or neo-arsphenamin in which analyses were not made daily, showed somewhat larger percentages of elimination.

The most recent work is that of Bergman.[6] He used the acid permanganate method of Lehmann for the destruction of organic matter in the urine and an original distillation and iodimetric method for determining arsenic. His paper is rather unique in that he studied the elimination of arsenic after minute doses of neo-arsphenamin, from 24 to 96 mg., and representing from 4.82 to 19.30 mg. metallic arsenic. He injected the drug both in a menstruum of the patients' own serums and in physiological solution of sodium chlorid.

In a series of three patients, using the smallest of these doses in menstruum of the patient's serums, he obtained the following percentage of elimination during the first three days following injection: 45.2,[7] and 45.2 per cent., respectively. With the largest of the doses the corresponding percentages were 18.7, 12.1, and 19.6. When the drug was dissolved in physiological solution of sodium chlorid and injected into three other patients in similar doses, the percentages of elimination were: 70.0, 39.8 and 53 with the smallest, and 48.0, 44.0 and 52 with the largest of the doses, respectively. Bergmann's work is intended to show that there is more rapid elimination, and, therefore, less storage when the drug is dissolved in saline, rather than in the patients' own serum. He recommends the latter method on the ground that there are fewer clinical "reactions" observed. It would seem to us that Bergmann has not studied a sufficient number of patients to warrant his conclusions. Moreover, when working with such minute amounts of arsenic, the errors in estimation and hence in calculation of percentages become very large.

METHODS OF INVESTIGATION

The present study was conducted on three cases of tertiary syphilis with optic atrophy. The patients were kept in a ward on a hospital diet and their water intake was controlled. Chemical studies of the blood which were made simultaneously have been reported in a separate communication by Weiss and Corson.[8] The injections of 0.6

6. Bergmann, H.: The Retention and Elimination of Arsenic After the Administration of Salvarsan in Serum and Aqueous Solutions, Biochem. Ztschr. **90**:348, 1918.

7. Data are given only for two days in which percentage eliminated is 24.9 per cent.

8. Weiss, C., and Corson, A.: Chemical Studies of the Blood and Urine of Syphilitic Patients Under Arsphenamin Treatment, Arch. Int. Med., 1921 (in press).

gm. doses of alkalized arsphenamin were always given at about 11 a. m. before breakfast. The drug was dissolved in about 120 c.c. of distilled water. The urines were collected quantitatively for twenty-four hour periods, preserved with toluene and analyzed within two or three days.

Before selecting the methods of analysis, including the technic for destruction of organic matter in the urine and the quantitative determination of minute amounts of arsenic, a comparative study was made by Messrs. Gavron, Blatt and one of the authors of this Institute of several existing methods, including those of Fresenius and von Babo and the Marsh-Berzelius as described by Hawk [9] and of the Scott [10] and Bang [11] methods. A modification of the Green [12] iodometric microtitration method was finally adopted. A description of this technic as well as analytical figures with the various methods tested will be found in a separate report by Raiziss, Gavron and Blatt.[13]

RESUMÉ AND ANALYSIS OF RESULTS

The details of the analyses, the intervals of injection and various notes concerning the patients are given in Tables 1 and 2. The dose was always 0.6 gm. of alkalized arsphenamin administered intravenously in 120 c.c. of distilled water, given fortnightly, weekly or semi-weekly, as described below.

CASE 1.—T. M., male, aged 38. Optic atrophy (Table 1). Chancre ten years ago. Under continuous arsphenamin treatment during the past two and one-half years.

This patient showed normal values for blood urea, sugar and nonprotein-nitrogen before this study was begun. The details of the subsequent changes in the blood will be found in a separate communication.[8] Very small amounts of arsenic were found in the urine before injection, this patient having been under continuous treatment for many years. The patient stated he always suffered mild reactions after injections. After this dose of 0.6 gm., there was nausea and occasional vomiting which lasted until the next morning. During the first, second and third days, the following amounts of arsenic were found in the daily twenty-four hour specimens of urine: 7.39, 3.12 and 1.47 mg. metallic arsenic, respectively. This is equivalent to an elimination of 6.3 per cent. in three days. During the succeeding ten days the amounts gradually diminished until they reached a level of about 0.11 mg. on the thirteenth and fourteenth days after the injection. A mild retention of nitrogen was indicated in the blood findings.

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9. Hawk, P. B.: Practical Physiological Chemistry, P. Blakiston's Son & Co., Philadelphia, 1918, pp. 476-478.

10. Scott, W. W.: Standard Methods of Chemical Analysis, D. Van Nostrand Co., New York, 1918, p. 30.

11. Bang, I.: Quantitative Determination of Arsenic in Urine, Farmaceutisk Revy, Schweiz. Apoth. Ztg. **55**:393, 1917.

12. Green, H. H.: The Microtitration of Arsenic, Union of South Africa Dept. Agriculture, Fifth and Sixth Reports, 1916-1918, of the Director of Veterinary Research, Pretoria **5**:541-550, 1918.

13. Raiziss, G. W.; Gavron, J. L., and Blatt, A. C.: The Estimation of Minute Quantities of Arsenic in the Urine (to be published).

A second dose of 0.6 gm. was given a fortnight after the first. The "reaction" this time was much more severe. There was vomiting, olyguria, bile-tinged urine, diarrhea and pain in the legs. The blood findings indicated a more definite nitrogen retention. During the first three days there were eliminated 9.79, 4.22 and 2.59 mg. metallic arsenic, respectively. This represents 8.8 per cent. elimination. The succeeding days showed gradually declining figures, reaching a level of from 0.53 to 0.58 mg. arsenic from the twelfth to the fourteenth days.

A third injection of 0.6 gm. arsphenamin was followed by a mild reaction—vomiting and headache—until the next morning. During the first three days the elimination was 7.46, 2.80 and 2.09 mg. arsenic, respectively, giving 6.56 per cent. There was evidence of mild retention of nitrogen in the blood during the next few days.

CASE 2.—M. J., male, aged 38. Optic atrophy (Table 1).

This patient showed values for total nonprotein nitrogen slightly above normal before this study was begun. He had been under continuous arsphenamin treatment for the past two years and showed small amounts of arsenic in the urine. After an injection of 0.6 gm. arsphenamin, there was a mild reaction characterized by vomiting. There was evidence of mild nitrogen retention in the blood following the injection. During the first three days, the amounts of arsenic eliminated in the urine were: 2.12, 4.33 and 2.07 mg., respectively. This is equivalent to 4.5 per cent. In the vomitus 0.85 mg. arsenic were detected. During the succeeding days the amounts of arsenic gradually fell, 0.69 mg. being found during the last days of the fortnight.

CASE 3.—K. W., male, aged 39. Optic atrophy (Table 1).

This patient had been under treatment for many years and showed traces of arsenic in his urine. His blood showed values of nonprotein nitrogen only slightly above normal. The injection of the first dose of 0.6 gm. arsphenamin was followed by slight chills, but no other untoward reaction. There was no evidence of increased nitrogen retention in the blood after this or any of the succeeding injections. During the first three days there were eliminated 3.10, 1.15 and 1.36 mg. arsenic, respectively, or 2.97 per cent. The amounts gradually diminished to small traces by the end of the fortnight. A second injection of 0.6 gm. was then given, and the following amounts were eliminated daily: 6.85, 2.61 and 1.49 gm. arsenic, or 5.8 per cent. in three days. A third dose was now administered with the following results: 5.13, 3.23 and 1.35 mg. arsenic, or 5.19 per cent. During the following days the figures were 2.61, 1.36, 1.57, etc., reaching a level of 0.44 mg. arsenic at the end of the fortnight.

DISCUSSION

A glance at Tables 1 and 2 reveals the fact that very small quantities of arsenic, detectable only by very delicate methods of analysis, are found daily in the urine of syphilitic patients after intravenous injections of arsphenamin. Thus, after a dose of 0.6 gm. containing from 187 to 188.6 mg. arsenic, from 3 to 8.8 per cent. was eliminated in three days and from 4.9 to 13.5 per cent. in the course of a fortnight. By far the greatest amount of arsenic eliminated by the route of the kidneys is, therefore, found in the urine of the first three days after injection. During the succeeding days the amounts gradually decline until by the fourteenth day they usually fall to a level of from 0.1 to 0.05 mg. which approaches the limit of accuracy of the method used.

Having seen that in human syphilitic patients only a relatively small portion of the arsenic injected intravenously as arsphenamin is elimi-

nated by the urine during the first week or two after administration, it would be of interest to know the degree of distribution and storage in the various tissues. No complete data are at hand giving the exact distribution of arsenic in all the organs of the human or animal body after a given dose of arsphenamin. We have been able, however, to obtain an approximate picture by making calculations, using some of the accurate figures on arsenic distribution available in the works of the Navassarts, Ullmann, Willcox and Webster, Lockemann, Bergmann and Green, and Vierordt's [14] excellent "anatomical, physiological and physical data and tables" as well as Stitt's "physiological normals" [15] which give the weights of the various organs of the human body. Our calculations show that the liver, the skeletal muscles and the skeleton, the kidneys, intestine and spleen are the most important depots for stored arsenic. In order of concentration, per 100 gm. of tissue, the liver is first, next the kidney and spleen and then the intestines. No data are available for some of the important human organs of elimination, such as the skin and lungs, as well as for other tissues, such as the heart, pancreas, omentum, etc. We have had to approximate these on the basis of published animal data and we have used the smallest figures,—0.5 mg. per 100 gm. of tissue.

A few striking facts from the literature deserve special comment at this place, the Navassarts,[3] as indicated above, have found the elimination in the feces to be from eight to ten times as great as that in the urine. The duration of elimination of measurable quantities of arsenic is about the same, from fourteen to twenty days. The arsenic in the feces may be due to resorption from the bile, as suggested by Obregia and Carniol [16] who detected arsenic in the bile twenty-five minutes after an intravenous dose of neo-arsphenamin. They also demonstrated the elimination of arsenic in the saliva. Pomaret [17] also found 10 mg. arsenic in 5 c.c. of dog's bile collected one hour after intravenous injection of 0.3 gm. neo-arsphenamin. The fact that we have found arsenic in the vomitus (Case 2), four hours after injection, suggests that elimination may take place by the route of the stomach, as in the case of morphin.

Willcox and Webster [4] found ½ and ⅓ mg. arsenic trioxid in 100 c.c. blood in two cases one hour after intravenous injection of 0.6 gm. arsphenamin.

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14. Vierordt, H.: Anatomische und physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediziner, Ed. 3, 1906, Jena.
15. Stitt, E. R.: Practical Bacteriology, Philadelphia, P. Blakiston's Son & Co., 1918, p. 540.
16. Obregia, A., and Carniol, A.: Sur l'elimination du neosalvarsan par la bile, Compt. rend. de la Soc. de biol. **78**:468, 1915.
17. Pomaret, M.: L'elimination des Arsenobenzols, La méd. **2**:123, 1920.

Myers [18] and Barbat [19] in a joint study conclude:

> The blood serum contains more than five times as much arsenic as the clot; it averages only 8 parts per million, or 0.8 mg. per 100 gm. of blood. This fact proves, that within half an hour after the administration of 0.4 gm. arsphenamin 75 per cent. is fixed in the body cells. Spinal fluid withdrawn immediately after injection showed 0.2 part arsenic per million of fluid in 42 per cent. of cases; 27 per cent. of the cases showed only traces of arsenic, and 31 per cent. were arsenic free. The spinal fluid withdrawn twenty-four hours after injection was arsenic free in one case out of twenty-six; two specimens showed traces of arsenic; the remaining twenty-three contained an average of 0.25 parts per million.

Ullman [1] found only questionable traces of arsenic in the perspiration of a patient treated with arsphenamin.

Young [20] in an interesting experimental study found, that if the serum of goats (previously injected with arsphenamin) is dialyzed, some of the arsenic is removed, but the rest is bound to the serum and can not be dialyzed nor does it give the usual qualitative tests for arsenic. Inorganic arsenic compounds do not behave in this way. Young concludes that it is the arsenic which is thus bound in the blood and tissues which is slowly eliminated in the urine and feces.

The duration of elimination of stored arsenic is a controversial subject. Some authors have detected traces of arsenic several months after the injection of a single dose of arsphenamin. Data on the intravenous method are meagre. Bailey and MacKay [21] in a study of syphilitics suffering from toxic jaundice as a result of treatment with novarsenobillion (French neo-arsphenamin) combined with mercury, were unable to detect any arsenic in the urines taken from twenty-four to 157 days after the last treatment. These authors used the Gutzeit test.

SUMMARY

The elimination of arsenic in the urine was studied in three cases of tertiary syphilis which were under arsphenamin treatment and under observation in a hospital ward. Very small quantities of arsenic, detectable only by very delicate methods of analysis, were found in the daily urine. Thus, after a dose of 0.6 gm. containing from 187 to 188.6 mg. arsenic, from 3 to 8.8 per cent. was eliminated in three days and from 4.9 to 13.5 per cent. in the course of a fortnight. By

18. Myers, C. N.: Determination and Distribution of Arsenic in Certain Body Fluids After the Injection of Arsenobenzol, Salvarsan and Neo-Salvarsan, U. S. Public Health Rep., Reprint No. 520, 1919 (May 2) pp. 881-890.

19. Barbat, J. H.: Permeability of the Meninges to Arsenic in Paresis and Tabes, J. A. M. A. **70**:147 (Jan. 19) 1918.

20. Young, W. J.: Fixation of Salvarsan and Neo-Salvarsan by the Blood After Intravenous Injection, Biochem. Jour. **9**:479, 1915.

21. Bailey, C. V., and MacKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment, Arch. Int. Med. **25**:628 (Nov.) 1920.

TABLE 1.—Daily Elimination of Arsenic in Urine of Syphilitic Patients Injected Intravenously with Arsphenamin

Patient	T. M.*			M. J.†	K. W.‡		
Drug injected	Arsphenamin			Arsphenamin	Arsphenamin		
Dose (each)	0.6 gm.			0.6 gm.	0.6 gm.		
Arsenic in doses injected	188.6 mg.			188.6 mg.	188.6 mg.		188.6 mg.
	Mg. Arsenic in Urine			Mg. Arsenic in Urine	Mg. Arsenic in Urine		
Days After Injection	First Dose	Second Dose	Third Dose	First Dose	First Dose	Second Dose	Third Dose
1	7.39	9.79	7.46	2.12	3.10	6.85	5.13
2	3.12	4.22	2.80	4.33	1.15	2.61	3.23
3	1.47	2.59	2.09	2.07	1.36	1.49	1.35
4	1.37	1.39	....	2.21	0.86	....	2.61
5	0.97	1.39	....	1.71	0.87	....	1.36
6	0.92	1.12	....	0.73	0.50	....	1.57
7	0.59	1.12	....	0.83	0.36	....	0.81
8	0.69	1.12	....	0.83	0.25	....	0.80
9	0.68	0.53	....	0.83	0.26	....	0.81
10	0.11	0.54	....	0.84	0.25	....	0.80
11	0.11	0.53	....	0.69	0.26	....	0.44
12	0.11	0.54	....	0.69	0.05	....	0.44
13	0.11	0.29	....	0.69	0.05	....	0.44
14	0.11	0.29	....	....	....	....	0.44
Total in first 3 days after injection	11.98	16.60	12.35	8.52	5.61	10.95	9.71
Percentage eliminated first 3 days	6.3%	8.8%	6.5%	4.5%	2.9%	5.7%	5.2%
Total elimination, entire period	17.75	25.46	12.35	18.57	9.34	10.95	20.23
Percentage eliminated entire period	9.4%	13.5%	6.5%	9.8%	4.9%	5.7%	10.9%

* This patient eliminated 3.14 mg. arsenic in urine during a three day period of observation just prior to first injection.

† This patient eliminated 9.81 mg. arsenic in urine during a six day period of observation just prior to injection and 0.85 mg. arsenic in vomitus four hours after injection.

‡ This patient eliminated 0.85 mg. arsenic in urine during a ten day period of observation just prior to first injection.

TABLE 2.—Summary of Data on Patients Studied

0.6 Gm. Doses of Arsphenamin (D. R. I.)* Alkaline Sol.	Values for Total N. P. N.† Observed Before Dose Was Injected	Clinical Reaction to Injection	Highest Values for Total N. P. N.† Observed After Injection	Total Mg. Arsenic Eliminated During First 3 Days After Injection	Percentage of Arsenic Eliminated in Urine During First 3 Days After Injection	Total Mg. Arsenic Eliminated During Interval Between Injections	Number of Days in This Interval	Percentage of Arsenic in This Interval
Case 1: T. M.; male; age 38. Optic atrophy								
First dose	24 to 30	Mild	39	11.98	6.3	17.75	14	9.4
Second dose	23	Severe	44	16.60	8.8	25.46	14	13.5
Third dose	35	Mild	38	12.35	6.5	12.35	3	6.5
Case 2: M. J.; male; age 28. Optic atrophy								
First dose	31 to 33.5	Mild	39	8.52	4.5	18.57	13	9.8
Case 3: K. W.; male; age 39. Optic atrophy								
First dose	28 to 35	None	31	5.61	3.0	9.34	13	4.9
Second dose	26.5	Very mild	35	10.95	5.7	10.95	3	5.7
Third dose	24.5	Very mild	24.7	9.71	5.2	20.23	14	10.9

* 0.6 gm. arsphenamin (D. R. I.) represents from 187 to 188.6 mg. arsenic.

† Values for total nonprotein nitrogen (N. P. N.) are given in mg. per 100 c.c. blood.

far the greatest amount of arsenic eliminated by the kidneys is, therefore, found in the urine of the first three days after injection. During the succeeding days the amounts gradually decline until by the fourteenth day they usually fall to a level of from 0.1 to 0.5 mg. which approaches the limit of accuracy of the method used.

The following observations deserve special comment:

1. Only a small part of the arsenic derived from arsphenamin is eliminated by patients through the urine, 13.5 per cent. being the highest amount in fourteen days.

2. The largest amount of arsenic is eliminated in the first three days; after that uniformly small amounts are found in the urine.

3. The elimination of arsenic is larger after the second and third doses are administered than after the first.

4. Using constant doses of 0.6 gm. arsphenamin, there is considerable variation in the amounts of arsenic eliminated during a given interval of time by any one patient as well as by different patients presumably in the same stage of the disease and treated under the same conditions.

5. The elimination of only small quantities of arsenic in the urine may be explained by the fact that a considerable quantity is eliminated through the feces and some is temporarily retained by the liver, kidneys, spleen, intestines and other parts of the body.

A review of the literature on arsenic elimination and storage, and of the fate of the arsphenamin molecule in the animal body is given.

We are indebted to Miss Anna Corson, B.Sc., for valuable assistance in this investigation.

A COMPARISON OF CAPILLARY AND VENOUS BLOOD IN PERNICIOUS ANEMIA

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Patients afflicted with pernicious anemia present many symptoms which differ strikingly from those of secondary anemia. One is the discrepancy between the general appearance of a patient with pernicious anemia and his blood count. Patients with secondary anemia having a red blood cell count of 2,000,000 or less, are not only weak and ill enough to be in bed, but have a pallor so marked as to be noticeable even to the most casual observer. In contrast with this, patients who have pernicious anemia may be up and around and may have color in the face and lips which is so good that one is often surprised at the finding of an extremely low red blood cell count, from 1,000,000 to 1,500,000. In fact, often their color is so good that the anemia is overlooked by their physicians. The pallor may be partly obscured by the lemon yellow tinge of the skin.

We have often wondered why patients with pernicious anemia retain their color so well. It might be accounted for, in part, by the fact that there is atrophy of the skin and mucous membranes which renders them abnormally transparent and thus they transmit well the red color of the little blood they possess.

It has seemed to us that there must be another factor, however, to account for this interesting phenomenon, namely, that possibly the red blood cells in this disease might have a tendency to lodge in the capillaries of the skin and therefore give a false impression concerning the gravity of the anemia. It seemed possible that one might determine whether or not this were a fact by estimating simultaneously the number of corpuscles in the capillary and venous blood and comparing the findings with those of normal blood.

We found a marked difference between the capillary and venous counts in all cases of pernicious anemia examined, whereas, in normal individuals the capillary and venous counts were practically the same. All the patients had a frank pernicious anemia with atrophy of the skin and mucous membranes, characteristic tongue, achylia and characteristic blood findings, with red cell counts of 1,000,000 or a little above when first examined. The high counts recorded were all due to the fact that the patients had been transfused some weeks or months prior to the time that the counts were made.

The capillary red blood cell count of patients with pernicious anemia was 1,264,000, or 19.3 per cent. higher on an average than the venous counts made at the same time. In every case there was a marked difference, the most marked being 3,070,000 red blood cells in the capillary blood and 1,920,000 in the venous blood—a difference

TABLE 1.—VENOUS AND CAPILLARY* BLOOD COUNTS IN PERNICIOUS ANEMIA

Date	Capillary Count	Venous Count	Reduction, per Cent.	Remarks
Case 1:				
Aug. 31, 1921.....	2,400,000	1,840,000	23.3	Transfused 10/5/20
Sept. 13, 1921.....	2,220,000	1,760,000	20.7	
Dec. 1, 1921.....	4,040,000	3,480,000	13.8	Transfused 10/10/21 and 10/28/21
Case 2:				
Oct. 25, 1921.....	5,440 000	4,800,000	11.8	Transfused 1/28/21
Case 3:				
July 29, 1921.....	3,380 000	2,280,000	32.5	Transfused 6/5/21 and 6/18/21
Oct. 7, 1921.....	5,200,000	3,880,000	25.3	
Case 4:				
Aug. 30, 1921.....	6,400,000	5,300.000	17.2	Transfused 3/21/21
Sept. 20. 1921.....	5,640,000	4,400,000	22.3	
Oct. 1, 1921.....	6,240.000	5,520,000	11.6	
Oct. 25, 1921.....	5,620,000	5,510,000	16.7	
Case 5:				
Nov. 28, 1921.....	2,240,000	1,600,000	28.5	Transfused 11/29/21
Dec. 4, 1921.....	3,440,000	2,680,000	22.0	
Case 6:				
Nov. 28, 1921.....	4,960,000	4,200,000	15.4	Transfused 1/21/21
Case 7:				
Nov. 28, 1921.....	3,070,000	1,920,000	37.4	Transfused 10/21/21
Case 8:				
Dec. 23, 1921.....	1,280.000	960,000	25.0	Transfused 12/31/21
Jan. 1, 1922.....	3,800,000	2,600,000	31.6	
Venous and Capillary Blood Counts in Normal Individuals:				
Case 1.....	5,520,000	5,540.000		
Case 2.....	4,960,000	5,120,000		
Case 3.....	5,260,000	5,400,000		
Case 4.....	5,160,000	5,000,000		
Case 5.....	6,080,000	6,120,000		
Venous and Capillary Blood Counts in Secondary Anemia:				
Case 1:				
Jan. 19, 1922.....	2,960,000	2,680.000	9.4	Transfused 1/28/22
Jan. 30, 1922.....	5,440,000	5,360,000	1.3	
Case 2:				
March 4, 1922....	2,400,000	2,480,000	None	
Case 3:				
Jan. 30, 1922.....	5,280,000	5,200,000	1.2	Transfused 9/7/21 prior to making of counts
Case 4:				
Jan. 30, 1922.....	4,400,000	4,720,000	None	Transfused 1/23/22 prior to making of counts

* In making the capillary blood count a small slit was made in the lobe of the ear and the blood drawn up in a red counting pipet in the usual manner. For the venous counts a small amount of blood was drawn from an arm vein into a syringe and a count quickly taken from this.

of 1,150,000, or 37.4 per cent., the least marked being 6,240,000 red cells in capillary blood and 5,520,000 red cells in venous blood, a difference of 770,000 red cells, or 11.6 per cent. This difference was striking regardless of whether the counts were made when the counts were low or whether they were made after treatment by transfusion when the counts were high. In contrast with this, the difference between

the capillary and venous counts in normal individuals was not great in any case and did not exceed 1.2 per cent. in a single instance, nor did it exceed 9.4 per cent. in four cases of secondary anemia, two of which had been transfused shortly before the counts were made.

It was noted that the venous blood of patients with pernicious anemia contained an increased proportion of small cells while the capillary blood contained an increased number of macrocytes. This difference between the venous and capillary blood was so striking as to leave no doubt as to its real existence. It has seemed to us that the large red cells of the blood of patients with pernicious anemia lag in the capillary bed while the smaller cells filter through and in this way account for the marked difference between the capillary and venous counts.

This view would be in harmony with physical laws which govern deposits made by streams of water which carry a sediment heavier than water. As a stream broadens it slows, its carrying power is thereby reduced, and part of its sediment is deposited. The larger particles of a given specific gravity are deposited first or lag along the creek bed while the smaller particles of the same gravity are carried on. We have a somewhat similar condition existing in the human body though modified no doubt by biologic laws. As blood reaches the capillary bed the stream broadens and slows. Furthermore, the pulse is lost. There should exist, therefore, a tendency for the larger red cells (which are heavier than serum) to lag and for the smaller ones to be carried along readily.

One could believe also that the larger red cells might be retarded in the capillary bed by a process of filtration. This may be a factor also but against this view is the fact that in only one of four cases of leukemia which we have examined was there a great difference between the capillary and venous white cell counts (lower specific gravity than red cells) in spite of the fact that the myelocytes were larger than the leukocytes and lymphocytes.

In the belief that more light might be thrown on the subject, capillary blood cell counts were made on four patients with pernicious anemia, two of whom (Cases 9 and 10) had been transfused several months previously. Blood was withdrawn from the arm veins without the use of a constricting tourniquet to distend the veins. After this blood was taken, a tourniquet was placed around the arm for one minute, tight enough (about 180 mm. of mercury) to prevent arterial blood from entering the arm and venous blood from escaping. During this minute the hand was contracted and relaxed a number of times with a view of dislodging, if possible, any red cells which might have accumulated in the capillaries of the arm. The muscular contractions forced the blood out into the veins so that they became quite tense. At the expiration of the minute, the tourniquet was

removed for about two seconds and then quickly replaced at 180 mm. of mercury. This was done for the purpose of allowing the blood in the veins to be replaced by blood from the capillary bed. Venous blood was then withdrawn and counts were made.

The results obtained by this procedure were quite interesting. In each instance the venous count taken while the arm was at rest and before a tourniquet was applied was much lower than the capillary counts taken from the lobe of the ear. The venous counts taken after constriction of the arm with tourniquets and exercise were higher in

TABLE 2.—CAPILLARY AND VENOUS COUNTS IN PERNICIOUS ANEMIA BEFORE AND AFTER CONSTRICTION OF THE ARM AND EXERCISE

Case	Capillary Counts	Venous Counts Before Constriction	Venous Counts After Constriction and Exercise
9	4,085,000	2,505,000	3,125,000
10	3,220,000	2,670,000	3,150,000
11	1,440,000	880,000	1,120,000
12	2,880,000	2,240,000	2,560,000

TABLE 3.—CAPILLARY AND VENOUS BLOOD COUNTS IN NORMAL PERSONS BEFORE AND AFTER CONSTRICTION OF THE ARM AND EXERCISE

Case	Capillary Counts	Venous Counts Before Constriction	Venous Counts After Constriction and Exercise
13	5,170,000	5,210,000	5,490,000
14	4,800,000	5,160,000	5,280,000
15	4,960,000	5,040,000	5,080,000
16	5,040,000	5,080,000	5,120,000

every instance than the venous counts taken while the arm was at rest—in fact, the difference was so marked in each instance that we feel sure had the venous counts been taken from veins without the aid of a tourniquet they would have been relatively lower than the ones obtained.

As a control, similar counts were made on four normal persons. The venous counts taken before and after constriction and exercise were essentially the same as the capillary counts.

We wish to suggest that the relatively good color of the skin and lips in patients with pernicious anemia might be accounted for, in part, by the fact that the capillary blood is richer in red corpuscles than the venous blood and for this reason is misleading and does not give the physician a correct idea of the gravity of the situation.

CONCLUSIONS

1. Capillary red blood cell counts on patients with pernicious anemia were on an average 17.6 per cent. higher than similar counts made

on venous bloods at the same time. The difference was as great as 37.4 per cent. in one case, and in every case it was 11.6 per cent. or more.

2. Venous counts made after constriction of the arm with a tourniquet, combined with exercise of the hand, were materially higher than counts made before constriction of the arm and when the hand was at rest.

3. An increased number of macrocytes was observed in capillary blood as compared with venous blood.

4. The striking difference between the capillary and venous counts is caused, we believe, by a tendency for the larger red blood cells (macrocytes) to lag in the narrow capillary bed where the rate of flow of blood is slow and the pulse is lost.

5. It is believed that this accounts, in part, for the circumstance that a patient with pernicious anemia may have relatively good color of skin and lips even though he may be gravely anemic. This is misleading and frequently obscures the real gravity of the situation.

We wish to thank Drs. L. S. Milne, L. F. Barney, J. T. Ferguson and A. J. Simpson for their kindness in referring Cases 2, 7, 10 and 11 to us for study.

STUDIES ON THE NATURE OF NONSPECIFIC PROTEIN IN DISEASE PROCESSES

IV. BLOOD FRAGILITY, RETICULATION AND BLOOD CHEMISTRY *

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The nature and mechanism of the reaction caused by the injection of foreign protein into the blood stream is still obscure. Some light has been thrown on this remarkable phenomenon by various workers who have studied the changes in blood cytology, certain phases of blood chemistry and immunology which occur during this reaction. The nature of this reaction is still a matter of controversy. There are some who consider the foreign protein reaction as an anaphylactic phenomenon. Others do not agree. There is still so much to be known about this subject that any further information is of interest and value. Cowie [1] in a very comprehensive review of the nonspecific protein reaction has summed up all the present day knowledge on this subject. Herewith we present a more detailed report of some studies on the blood following the intravenous injection of a nonspecific protein. We have investigated blood fragility, reticulated red cells, blood urea, nonprotein nitrogen, blood sugar and alkali reserve in patients who were being treated by intravenous protein injections as a therapeutic measure for arthritis, chorea and various eye infections. The doses varied from 100 to 750 million killed typhoid bacilli. The patients all reacted characteristically with chill and rise in temperature. The ages of the patients varied from 8 to 50 years.

Fragility of the Red Blood Cells.—The method of Greenthal and O'Donnell [2] was used. Six patients were studied. In one case four fragility determinations were made at varying intervals after the injection. Our results show a slight increase in fragility following foreign protein injections. In Case 4 the control determination showed an increased fragility. This patient, a man with an infected corneal ulcer, had received four injections of protein during the previous ten days. It is possible that these injections may have made his red blood

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1. Cowie, D. M.: New York State J. M. **21**:395, 1921.
2. Greenthal and O'Donnell: Am. J. Dis. Child. **22**:212, 1921.

cells more fragile. Raphael and Sherman,[3] using the same method, in a study of the fragility of the erythrocytes in psychopathic patients receiving foreign protein injections likewise found a slight increase in fragility after the injection. At any rate the increase is not marked enough to be of significance (Table 1).

The percentage of reticulated red cells before and at intervals following the protein injection was determined in eight patients. The patients were examined during various injections, one during the first injection, three during the second and third, and one during the sixth injection. At no time during the protein paroxysm were we able to find any marked change in the number or character of these cells. They were always within normal limits. This was contrary to our expectations as examination of the blood smears after protein injec-

TABLE 1.—EFFECT OF FOREIGN PROTEIN ON THE FRAGILITY OF THE RED BLOOD CELLS

Case	Control	After Injection	Remarks
1	0.425-0.325*	0.450-0.325	Blood drawn 1 hour after injection, during chill; temperature 101 F.
2	0.425-0.325	0.425-0.325	Four hours after injection, temperature 102.6 F.
3	0.425-0.300	0.425-0.325	Six hours after injection, temperature 101.8 F.
4	0.450-0.350	0.450-0.375	Three hours after injection, fifth injection of foreign protein; increased fragility due to repeated injections?
5	0.425-0.325	0.450-0.350	Four hours after injection, temperature 104 F.

Case	Control	½ Hour	1½ Hours	3 Hours	5 Hours
6	0.425-0.325	0.450-0.325	0.450-0.325	0.475-0.350	0.425-0.325

* 0.425-0.325 = Beginning hemolysis, 0.425 per cent. saline, to complete hemolysis, 0.325 per cent. saline.

RETICULATED RED BLOOD CELLS

Method: Capillary pipets were coated and dried with several layers of a vital blood stain (Unna's polychrome methylene blue, in citrated saline solution). The blood was quickly drawn into the capillary tubes and after from ten to twenty minutes a drop was blown on a slide and examined. Six hundred cells were counted each time. The efficacy of the stain was determined by examining the blood of normal adults and infants, patients with simple anemias, and one case of hemolytic family icterus.

tions shows an increase in nucleated red cells, blood platelets and myelocytes. If the reticulated red cell is an embryonal cell, one might think that there would be an increase during the protein reaction, for the bone marrow is stimulated to send forth new cells. However, in none of the patients, both children and adults, were the reticulated cells increased with large doses of dead typhoid bacilli (Table 2).

3. Raphael and Sherman: Am. J. Psychol. **1**:31, 1921.

Urea Nitrogen.—The results of the blood analysis show nothing remarkable during the protein paroxysm. The urea nitrogen was within normal limits at all times. It made no difference whether the determinations were made during the first or eighth injection of typhoid vaccine. There was a slight rise in the urea nitrogen usually between four and eight hours after the injection. This corresponded usually with the highest temperature. It does not seem as though the intravenous injection of typhoid protein causes any appreciable change in the urea nitrogen of the blood. Certainly it was not above normal limits in any reaction. Hisanabu [4] found a marked increase in the urea nitrogen of the blood of guinea-pigs during peptone intoxication and

TABLE 2.—EFFECT OF FOREIGN PROTEIN ON THE PERCENTAGE OF RETICULATED RED CELLS

Before Injection		Hours After Injection											
Case	Control	½	1	1½	2	2½	3	4	5	6	7	8	Remarks
1	0.7*	1.4	...	1.2	1.0	...	1.4	0.6	...	0.9	1.0	...	1st injection 300 million bacilli
2	0.6	0.6	0.5	0.3	0.8	0.6	0.7	0.6	0.4	0.6	0.5	0.7	2d injection 300 million bacilli
3	0.6	...	0.6	...	0.3	...	...	0.2	0.3	0.5	0.4	0.4	3d injection 500 million bacilli
4	1.2	1.1	0.8	0.6	0.7	0.6	1.0	0.8	1.1	0.8	0.6	0.8	2d injection 500 million bacilli
5	1.0	0.4	0.2	0.3	0.5	0.8	...	0.4	0.6	...	0.6	...	3d injection 750 million bacilli
6	1.6	1.2	1.0	1.5	1.1	1.2	1.6	1.4	1.8	1.1	1.4	1.6	2d injection 500 million bacilli
7	1.4	1.8	0.5	0.9	0.6	1.4	1.2	1.1	1.2	...	...	...	3d injection 750 million bacilli
8	0.6	0.5	0.2	0.6	0.5	0.4	0.3	0.5	...	0.6	0.5	0.4	6th injection 500 million bacilli

* Expressed in per cent.

UREA NITROGEN AND TOTAL NONPROTEIN NITROGEN

Method: The urea nitrogen of the blood was determined by the Van Slyke-Marshall method. The total nonprotein nitrogen was determined by the method of Folin and Wu. On some of the patients both the urea and total nonprotein nitrogen were determined at the same time. On others only one of the two determinations was performed. The patients on whom the determinations were made were fasting during the time of the experiment. A blood sample was drawn in the morning, after a twelve-hour fast, and then the typhoid vaccine injected. Blood was then drawn at varying intervals during the day. The experiments were made at various injections.

anaphylactic shock. The negative results in these experiments suggest that so-called protein shock is an entirely different phenomenon from anaphylactic shock or peptone poisoning (Table 3).

Total Nonprotein Nitrogen.—The results of these experiments agree closely with those on the urea nitrogen. There is very little evidence of protein destruction in the body during the protein paroxysms as

4. Hisanabu: Am. J. Physiol. **1**:357, 1919.

TABLE 3.—Effect of Ffreign Protein on the Urea Nitrogen of the Blood

Before Injection		Hours After Injection											
Case	Control	½	1	1½	2	3	4	5	6	7	8	9	10	Remarks
1	16.5*	....	16.2	....	15.0	18.6	12.0	15.6	18.0	14.2	18.0	15.6	....	1st injection 350 million typhoid bacilli
2	7.8	....	....	8.9	....	9.6	....	10.1	....	9.8	....	9.6	....	2d injection 500 million bacilli
3	15.0	17.8	....	....	19.2	....	....	12.0	....	....	15.1	....	....	4th injection 600 million bacilli
3	12.6	....	....	13.2	....	....	13.4	....	....	....	....	15.0	....	5th injection 600 million bacilli 5 days later
4	10.1	....	14.2	....	7.2	11.4	10.2	16.2	15.0	8.6	8.4	9.6	....	2d injection 500 million bacilli
5	7.5	....	7.5	....	7.6	....	....	13.4	....	....	....	9.6	....	1st injection 400 million bacilli
6	7.7	....	....	....	8.4	....	11.7	....	11.2	....	9.5	....	9.2	3d injection 750 million bacilli
7	15.1	....	14.2	....	....	16.2	....	....	16.2	....	....	16.8	....	1st injection 300 million bacilli
7	10.2	....	9.2	....	12.0	....	10.8	....	....	....	11.4	....	....	2d injection 500 million bacilli 4 days later
8	10.6	....	13.5	....	11.7	....	17.3	16.2	10.1	13.7	....	9.7	9.5	7th injection 600 million bacilli
9	13.4	....	....	....	10.1	....	7.8	....	10.6	....	16.8	....	12.3	1st injection 400 million bacilli

* Expressed in Mg. per 100 C.c.

TABLE 4.—Effect of Foreign Protein on the Total Nonprotein Nitrogen of the Blood

Before Injection		Hours After Injection										
Case	Control	½	1	2	3	4	5	6	7	8	9	10	Remarks
1	34.6*	....	38.1	36.1	23.1	33.6	37.5	34.8	34.8	25.2	31.2	....	8th injection 600 million
2	25.4	....	....	22.8	....	24.3	....	24.1	....	27.3	....	26.7	3d injection 700 million
3	29.9	....	30.0	28.7	28.4	39.8	....	29.6	28.1	....	26.0	....	2d injection 500 million
4	32.9	23.1	....	25.7	....	21.1	....	....	....	29.5	....	....	4th injection 600 million
5	19.6	19.6	21.4	18.7	....	19.6	....	17.6	....	....	....	22.5	5th injection 600 million
6	27.5	....	36.6	37.5	36.6	38.1	33.9	35.7	37.5	30.0	33.1	....	1st injection 350 million
6	26.0	....	30.5	....	33.6	....	29.0	....	30.4	....	26.4	....	2d injection 500 million
6	22.9	....	....	....	22.1	....	....	....	33.2	....	31.6	....	3d injection 600 million
7	34.0	....	....	33.6	....	30.4	....	25.6	....	31.5	....	26.2	1st injection 400 million
8	26.1	25.7	....	26.1	....	23.4	....	....	....	23.4	....	24.4	1st injection 300 million

* Expressed in Mg. per 100 C.c.

would be shown by an increase in the non-protein constituents of the blood. The very slight increase in non-protein nitrogen between the fourth and eighth hours can probably be accounted for by the fever which was highest at that time. Hisanabu found a marked increase in nonprotein nitrogen in the blood of guinea-pigs who were suffering from anaphylactic shock. Jobling [5] found some increase in the non-protein nitrogen after the intravenous injection of dead typhoid bacilli. Working with rabbits Pepper and Miller [6] found no change in the total nitrogen and urea of the urine after a single intravenous injection of dead typhoid bacilli. The results of the urea and non-protein nitrogen analyses of the blood of patients after the intravenous injection of dead typhoid bacilli form substantial evidence against the theory that protein and anaphylactic shock are similar (Table 4).

Carbon Dioxid Capacity of Blood Plasma.—The method of Van Slyke was used. Three patients were studied after the foreign protein injections, two during the first injection and one during the fifth injection. The results of these experiments show that there is a slight diminution in the alkali reserve of the blood plasma during the protein paroxysm. This we think is not great enough to be of any practical importance. We have never seen any of our patients show any serious symptoms of acidosis. Eggstein [7] studied the alkali reserve during protein and anaphylactic shock. He quotes the result of one experiment on man. A patient given twenty million dead typhoid bacilli into the vein showed a carbon dioxid capacity of 45.9 volumes per cent. one hour after the injection. Her carbon dioxid capacity before the injection was 55.8 volumes per cent. In animals a much severer grade of acidosis was produced. This could be overcome by the injection of sodium bicarbonate. In anaphylactic shock in animals the acidosis was so marked as to endanger life. Death could not always be prevented by the use of sodium bicarbonate. Here, again, we find a difference between so called protein and anaphylactic shock (Table 5).

Blood Fat.—Cowie and Hoag [8] have shown in their studies on blood fat [1] that the total lipoids decrease during the protein paroxysm induced by the intravenous injection of dead typhoid bacilli apparently to a more marked degree than they do in fasting subjects who have not received an injection of foreign protein. We are indebted to them for the privilege of reporting their detailed results here (Table 6).

Blood Sugar.—The method of Folin and Wu was used. Six patients were studied at various injections. The patients were fasting during the period of observation. The results of the blood sugar

5. Jobling: J. A. M. A. **65**:515 (Aug. 7) 1915.
6. Pepper and Miller: J. Infect. Dis. **17**:694, 1916.
7. Eggstein: J. Lab. & Clin. M. **6**:481, 555, 1921.
8. Cowie and Hoag: J. A. M. A. **77**:1493 (Nov. 5) 1921.

experiments show nothing remarkable. There is a slight rise in the blood sugar during the height of the fever which quickly returns to normal. We have also run blood sugar analyses by the Benedict method on the same blood samples. They also give the same readings always, however, somewhat higher than with the Folin test. The rea-

TABLE 5.—Effect of Foreign Protein on the Carbon Dioxid Capacity of the Blood Plasma

Before Injection		Hours After Injection								
Case	Control	½	1	2	3	4	5	8	24	Remarks
1	55.7*	51.9	57.6	54.6	47.5	50.0	50.1	51.2	54.8	1st injection 300 million
2	52.0	54.8	53.8	51.2	50.0	46.5	51.8	51.6	53.8	1st injection 600 million
3	58.7	57.9	56.1	55.6	52.2	55.7	....	56.3	56.0	5th injection 600 million; very little reaction

* Expressed in volume per cent.

TABLE 6.—Effect of Foreign Protein on Blood Lipoids

Before Injection		Hours After Injection									
Case	Control	½	2	3	4	5	6	7	8	9	Remarks
1	0.793*	0.811	0.793	0.798	0.756	0.756	0.753	0.757	0.715	0.722	Fasting; 3d injection 500 million
2	0.716	0.639	0.644	0.540	0.577	0.655	0.670	0.690	0.684	0.716	Fasting; 1st injection 600 million

* Expressed in per cent.

TABLE 7.—Effect of Foreign Protein Injections on the Blood Sugar

Before Injection		Hours After Injection											
Case	Control	½	1	2	3	4	5	6	7	8	9	10	Remarks
1	0.098*	0.111	0.116	0.102	.....	.....	.....	0.120	.....	.....	.....	.....	1st injection 300 million
2	0.105	.....	.....	0.110	.....	0.129	.....	0.137	.....	0.135	.....	.....	3d injection 600 million
3	0.081	0.085	0.081	.....	0.000	.....	0.120	.....	.....	.....	0.080	.....	5th injection 500 million
4	0.101	.....	0.110	.....	0.120	.....	0.114	.....	0.115	.....	.....	.....	2d injection 500 million
5	0.108	.....	0.106	0.082	0.088	0.123	0.140	0.122	0.129	.....	.....	0.117	3d injection 400 million
6	0.105	.....	.....	0.102	.....	0.087	.....	0.083	.....	0.119	.....	0.108	1st injection 350 million

* Expressed in per cent.

son for the increased blood sugar during the fever is not clear. One might surmise that it is due either to increased metabolism or to stimulation of the glycogen reserve (Table 7).

Our investigation of the blood changes after an intravenous injection of foreign protein (typhoid vaccine) lead us to the following conclusions:

CONCLUSIONS

1. There is a slight increase in the fragility of the red blood cells during the protein paroxysm.

2. There is no change in the percentage of reticulated erythrocytes.

3. There is a moderate rise in the urea and total nonprotein nitrogen of the blood at the height of the fever resulting from the protein injection.

4. There is a moderate fall in the alkali reserve of the blood after the foreign protein injection. This is of short duration and a normal reading is soon obtained.

5. There is a decrease in total blood lipoids during the protein shock. This decrease is perhaps more marked than that which is found in fasting subjects not receiving the protein.

6. There is a slight rise in the blood sugar curve (Folin and Bendict) at the height of the reaction following the protein injection.

7. We believe that the so-called protein shock and anaphylactic shock are different phenomena.

DIETETIC TREATMENT OF CHRONIC ARTHRITIS AND ITS RELATIONSHIP TO THE SUGAR TOLERANCE *

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The importance of diet in the treatment of chronic arthritis is a question on which there is today considerable difference of opinion. In practice, its effect, as a rule, is confused by the establishment of several forms of treatment at one time, such as the removal of infectious foci, rest in bed, electrotherapy and hydrotherapy and other hygienic measures. It is, however, the experience of many observers that improvement is often brought about by changes in diet alone. But as to the character of this change, difference of opinion also exists. Increase in diet is recommended by some and decrease by others, or reduction of proteins in one case and reduction of carbohydrates in another. Sometimes improvement has been so marked as to lead older clinicians to believe that the disease had a metabolic basis, but clinical and laboratory investigation has not offered much evidence to support this hypothesis. In fact, interest has been more directed toward the part played by bacteria in the causation of this disease, and recent work has resulted in the general belief that chronic arthritis—with the exception of those cases due to trauma, strain, gout, some neuropathy, scurvy and hemophilia—is the result of a bacterial process. It is, therefore, natural that the origin of such infection should be looked for, infectious foci removed, vaccines administered, and, if necessary, some form of nonspecific protein therapy utilized. These measures are often attended by marked success, but sometimes results are disappointing, and if improvement occurs, it is often of a temporary nature.

In spite of this belief that the condition is a bacterial disease, there are still clinicians who insist on the importance of diet in its treatment. Pemberton,[1] especially, has for many years advised careful dietetic regulation—recommending a general reduction of the food intake, and laying special stress on the restriction of carbohydrates. In our own clinic, we have been impressed with the value of this recommendation in many cases. And, further, in those cases which receive benefit from such treatment, there has been as much clinical evidence of infection as in those which are refractory to such measures. One case, in which

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1. Pemberton, R.: Use of Diet in Treatment of Chronic Arthritis, Am. J. M. Sc. **161**:517 (April) 1921.

a hemolytic streptococcus was isolated from the blood during the height of the arthritis, showed prompt and quite marked improvement with a sudden reduction of diet. This reduction was made about six weeks after the onset of the attack, while the patient was still in a febrile state, and the favorable course of the infection was undoubtedly brought about by the change in diet. It would seem, then, that in such cases, there is a relationship between the maintenance of an infection and an unsuitability of the diet to the patient. This unsuitability might be due either to actual lack of balance in selection of food or to some error in the metabolism of the patient.

In a metabolic study of chronic arthritis, Pemberton and Foster [2] observed that the rise in blood sugar, following the administration of 100 gm. glucose, was both increased and prolonged. They further concluded that this lowering of sugar tolerance was roughly an indication of the severity of the disease—tending to return to normal as convalescence set in. If this were the case, a determination of sugar tolerance would not give any specific information bearing on a case, other than its severity, but our own figures were not in accord with this conclusion, for it was sometimes found that some of the mildest cases showed a well-marked decrease in the sugar tolerance, which might even persist after recovery, while cases of the severest type sometimes gave figures which varied but slightly from normal. This question then presented itself: Does the lowering of sugar tolerance call for reduction of diet, and is the degree to which this tolerance is lowered any indication of the probability of giving relief by such measures? With this question in mind, we present the records of 100 cases of chronic arthritis in which the sugar tolerance was determined and in which the effect of reduction of diet alone was studied.

Method of Treatment.—The 100 cases represent a selection from 160 cases of nonpurulent arthritis admitted to the medical wards of the Toronto General Hospital, and a few cases seen outside. The remaining sixty cases could not be included for various reasons. Many patients recovered without special treatment; a few recovered after removal of some focus of infection; others left the hospital before treatment was adequately observed. The cases associated with gonococcal infections are not included. Following McCrae's [3] classification, the majority of cases were of the periarticular type, with or without deformity; a few showed hypertrophic bone changes, and one or two cases showed both types of the disease. The duration of the condition is shown in the tables, and in no case was dietetic treatment started before six weeks after the onset. The patients who were

2. Pemberton, R., and Foster, G. L.: Arch. Int. Med. **25**:243 (March) 1920.
3. McCrae: Oxford Med. **4**:374, 1921.

admitted to hospital were allowed to remain in bed for two weeks at least, and until the process appeared to have reached a more or less stationary stage. This was done because rest alone may result in considerable improvement or even recovery. A few patients were treated outside of hospital, and in these no changes were made in the manner of living, other than the change in diet.

Dietetic treatment was carried out as far as possible in a routine manner, without regard for the patient's tolerance for carbohydrates or for his former diet. At first various changes in diet were tried. Reduction of the carbohydrates to one fifth or less of the usual intake sometimes was followed by much improvement. But better results were obtained by a more general reduction, and the large majority of the 100 patients were treated in the following manner: three glasses of milk, 3 glasses of buttermilk, one-half grape fruit and one or two oranges a day for one week; then the gradual addition of such food as eggs, fish, fowl, meat, 5, 10 and 15 per cent. vegetables, fruits, junkets and jellies; and finally, brown bread in small amounts. Patients who were underweight were allowed cod liver oil and cream. This increase was made so as to provide from 1,500 to 2,000 calories a day within four weeks' time. The improvement noted in the tables occurred within this period, and with one or two exceptions, if no progress had been observed, it was not found worth while to continue. But those who did well were recommended to adhere to the diet—many reported progress for several months, and a few found that a relapse set in if their former diet was indulged in too freely.

While the effect of this treatment was being observed, no other form of treatment was given. If foci of infection were removed, four weeks were allowed to pass, but often these foci were untouched until after the period of observation. No drug was given, and physiotherapy was not ordered. When necessary, the bowels were moved on alternate days by enemas, and in a few cases liquid petrolatum was given by mouth.

The Sugar Tolerance.—The test was carried out as recommended by Hamman and Hirschman.[4] After a fast of fifteen hours, 100 gm. glucose was given by mouth in 300 c.c. of water, with the addition of the juice of half a lemon; 250 c.c. of water was given at one and two hour intervals. Blood sugar determinations were made immediately before the administration of the sugar and one-half hour, one hour, two hours and three hours afterward. The half-hour determination did not appear to give any essential information in most cases, and was discontinued. In a few cases, it was convenient to obtain blood at one

4. Hamman, L., and Hirschman, F. I.: Alimentary Hyperglycemia and Glycousuria as a Test for Sugar Tolerence, Arch. Int. Med. **20**:761 (Nov.) 1917.

and one-half hour intervals only—these two determinations being usually sufficent to establish the existence of definite lowering of the tolerance. All the determinations were done by the method of Folin and Wu,[5] the blood, as a rule, being precipitated at the bedside and the colorimetric reading done the same day; the figures are given in mg. per c.c.

For the interpretation of the blood sugar readings, after the ingestion of 100 gm. glucose, it appears that three aspects are to be considered: (1) the maximum figure obtained; (2) the time at which the maximum occurs, and (3) the time required for the return to normal. There is still some disparity as to what should be considered a normal reaction. In our own work, a figure above 1.7 or a failure to return to the original level in ninety minutes, has been taken as a disturbance in sugar tolerance. In health, the maximum is reached in less than sixty minutes. In many of the figures presented, the maximum occurred later than this, but as this point possibly was frequently missed, it cannot be considered specially. The striking characteristic of the figures presented is the height which many of the figures reached, and especially the delay in the return. This last point is well brought out by the method of determining the blood sugar at one hour or one hour and a half intervals. For purposes of comparison, an average was taken of the figures obtained after the administration of the glucose, either at the hour or at one hour and a half intervals. These averages take into account both the maximum reached and the delay in the return, and in the tables the cases are grouped according to these averages. Three arbitrary groups were selected: (1) those in which the average was less than 1.4; (2) those in which the average was from 1.4 to 2, and (3) those in which the average was greater than 2.

Table 1 shows that the figures obtained varied from those which fell within normal limits to those which might be considered as indicating frank diabetes. And, indeed, no line can be drawn so as to classify the cases into diabetics and nondiabetics. Of the 100 cases, twenty-four belonged to Group I; i. e., with the average of the figures obtained under 1.4; fifty-six belonged to Group II, with an average of from 1.4 to 2, and twenty belonged to Group III, with an average greater than 2.

As to the relationship of the sugar tolerance to the severity of the disease, none was found; as many mild cases were found to appear in the group with the low tolerance as in the group with the high tolerance; of the twenty most severe cases, six belonged to Group I, ten to

5. Folin, O., and Wu, H.: System of Blood Analysis; a Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

TABLE 1.—Cases in Which the Blood Sugar Averaged Less Than 1.4 Mg. per C.c. for Three Hours After Administration of 100 Gm. Glucose

Case	Sex	Age	Duration Before Admission	Fasting Blood Sugar	½ Hour	1 Hour	1½ Hours	2 Hours	3 Hours	Average	Result of Treatment
1	M	23	9 mos.	0.86	....	1.25	....	1.21	1.03	1.16	Improved
2	F	30	2-3 yrs.	1.06	....	1.18	....	1.17	1.05	1.13	Improved
3	F	39	3 mos.	0.82	....	0.96	....	1.30	1.10	1.11	No improvement
4	M	38	18 yrs.	0.98	....	1.37	....	1.45	1.36	1.39	Improved
5	M	29	8 mos.	1.05	1.07	1.73	....	1.07	1.16	1.32	No improvement
6	M	38	4 yrs.	0.84	1.34	1.49	....	1.29	1.23	1.39	Improved
7	M	26	6 mos.	0.99	1.47	1.58	....	1.44	0.71	1.24	No improvement
8	F	20	2 mos.	1.11	....	....	1.57	....	0.94	1.25	Recovered
9	F	31	10 yrs.	1.15	....	1.51	....	0.75	1.19	1.15	Improved
10	F	63	30 yrs.	1.09	....	1.55	....	1.20	0.94	1.23	No improvement
11	M	32	2 wks.	0.99	....	1.87	....	1.02	1.16	1.35	Improved
12	M	56	3 yrs.	0.93	....	1.63	....	1.73	0.76	1.37	Improved
13	F	55	6 wks.	1.28	....	....	1.17	....	1.19	1.18	Improved
14	F	61	5 yrs.	1.05	....	1.70	....	1.11	0.90	1.23	Improved
15	F	56	1 yr.	1.25	....	1.30	....	1.70	1.05	1.34	Much improved
16	M	27	6 yrs.	1.26	....	1.75	....	0.95	0.79	1.16	No improvement
17	M	34	20 yrs.	0.93	....	1.39	....	1.46	1.21	1.35	No improvement
18	M	33	2 yrs.	1.10	....	1.33	....	0.97	0.74	1.01	No improvement
19	M	30	2 yrs.	0.91	....	1.34	....	0.69	0.67	0.90	No improvement
20	M	26	4 yrs.	0.95	....	1.33	....	0.77	0.77	0.95	No improvement
21	M	65	10 yrs.	1.21	....	....	1.44	....	0.91	1.17	No improvement
22	M	40	6 mos.	1.25	....	1.74	....	1.32	1.11	1.39	Improved
23	M	60	8 mos.	1.09	....	1.27	....	1.06	1.24	1.19	No improvement
24	F	33	18 mos.	1.12	....	....	1.00	....	0.80	0.9	Much improved

Cases in which the Average was 1.4-2 Mg. Per C.c.

25	F	29	10 yrs.	1.2	....	1.8	....	1.7	1.5	1.6	Much improved
26	F	38	4 yrs.	1.3	....	1.7	....	1.8	1.3	1.6	Much improved
27	F	38	1½ yrs.	1.1	....	1.3	....	1.8	1.75	1.61	Much improved
28	M	20	8 wks.	1.1	....	1.5	....	1.9	1.3	1.42	Much improved
29	F	37	2 yrs.	1.08	1.17	2.04	....	1.99	1.05	1.69	No improvement
30	F	35	3 mos.	1.12	1.03	2.12	....	2.17	1.37	1.88	Much improved
31	M	40	3 yrs.	0.97	1.56	1.82	....	2.54	1.55	1.97	Improved
32	F	32	1 yr.	0.94	1.09	2.22	....	1.97	0.63	1.60	Much improved
33	M	54	7 wks.	1.09	1.83	2.31	....	1.85	1.75	1.97	Much improved
34	F	34	3 yrs.	1.05	....	....	2.10	....	1.60	1.85	Improved
35	F	39	2 mos.	1.07	....	....	1.45	....	1.46	1.45	Much improved
36	M	17	2 mos.	1.12	1.47	1.87	....	1.71	1.44	1.67	Much improved
37	F	28	6 wks.	1.04	....	....	1.73	....	1.34	1.53	Recovered
38	F	48	20 yrs.	0.87	....	1.52	....	1.67	1.19	1.46	Improved
39	F	60	1 yr.	0.93	....	1.86	....	1.26	1.25	1.45	Much improved
40	F	35	2 yrs.	1.24	....	1.98	....	1.61	1.18	1.59	Improved
41	F	24	1 yr.	1.08	....	1.58	....	1.53	1.51	1.54	No improvement
42	F	40	2 wks.	0.88	....	1.62	....	1.91	1.64	1.72	Much improved
43	F	60	15 yrs.	1.10	....	....	1.75	....	1.44	1.59	Improved
44	F	28	4 yrs.	1.65	....	1.94	....	1.54	0.97	1.48	Much improved
45	F	58	8 yrs.	1.03	....	1.67	....	1.67	1.65	1.66	Improved
46	M	23	7 yrs.	1.10	....	1.75	....	1.50	.50	1.58	Much improved
47	F	35	11 yrs.	1.17	....	1.98	....	1.42	1.22	1.54	Improved
48	M	35	1 yr.	1.3	....	2.0	....	1.5	1.4	1.6	Much improved
49	F	52	18 mos.	1.03	....	2.50	....	1.90	0.90	1.7	Much improved
50	F	45	2 wks.	0.95	....	2.54	....	2.13	1.22	1.65	Recovered
51	M	45	10 yrs.	1.17	....	2.16	....	1.87	0.94	1.65	No improvement
52	M	50	2 yrs.	1.3	....	1.5	....	2.2	1.3	1.6	Improved
53	F	29	6 wks.	1.2	....	2.15	....	1.6	0.95	1.56	Improved
54	M	49	2 yrs.	1.1	....	2.2	....	1.55	1.1	1.61	Improved
55	F	36	8 wks.	1.3	....	2.0	....	1.5	1.4	1.61	Much improved
56	M	47	9 mos.	1.08	....	2.20	....	1.68	1.85	1.91	Much improved
57	F	54	1 yr.	1.13	....	....	2.27	....	1.33	1.80	Much improved
58	M	57	8 yrs.	1.12	....	....	2.07	....	1.74	1.90	No improvement
59	F	34	5 wks.	1.29	....	1.53	....	2.20	1.41	1.71	Recovered
60	M	42	1 yr.	1.13	....	2.00	....	1.47	0.95	1.47	Much improved
61	M	30	5 yrs.	1.29	....	2.08	....	2.08	1.34	1.82	Much improved
62	M	47	7 wks.	1.08	....	2.20	....	1.68	1.85	1.91	Much improved
63	F	35	1 yr.	2.18	....	2.20	....	1.98	1.38	1.85	Improved
64	F	30	1 yr.	1.18	....	2.41	....	1.92	1.29	1.87	Improved
65	F	26	8 mos.	1.07	....	2.42	....	1.98	1.36	1.92	Improved
66	F	22	6 wks.	1.00	....	2.00	....	3.10	1.40	1.83	Recovered
67	F	43	6 mos.	1.2	....	2.3	....	1.85	0.75	1.10	No improvement

TABLE 1 (CONTINUED).—CASES IN WHICH THE AVERAGE WAS 1.4-2 MG. PER C.C.

Case	Sex	Age	Duration Before Admission	Fasting Blood Sugar	½ Hour	1 Hour	1½ Hours	2 Hours	3 Hours	Average	Result of Treatment
68	F	45	2½ mos.	0.95	....	....	2.68	....	1.11	1.89	No improvement
69	M	35	2 yrs.	0.91	....	2.59	....	2.11	1.28	1.99	No improvement
70	M	31	6 mos.	1.02	....	2.35	....	2.0	1.5	1.88	No improvement
71	M	36	6 mos.	1.3	....	2.7	....	1.7	0.7	1.7	Much improved
72	M	52	6 mos.	1.5	....	2.5	....	1.3	1.3	1.7	Much improved
73	F	37	8 yrs.	1.25	....	....	1.56	....	1.67	1.62	Much improved
74	F	65	1 yr.	1.28	....	2.44	....	1.79	1.16	1.79	Much improved
75	F	66	Many years	1.02	....	2.66	....	1.27	1.28	1.53	Much improved
76	M	34	1 yr.	0.98	....	2.02	....	2.17	1.32	1.83	Improved
77	F	69	10 yrs.	1.09	....	1.96	....	1.56	1.20	1.57	Improved
78	F	53	2 yrs.	1.45	....	....	1.91	....	1.64	1.77	Improved
79	M	36	6 yrs.	1.2	....	2.1	....	2.25	0.9	1.75	Much improved
80	F	49	10 yrs.	1.2	....	2.0	....	1.9	0.9	1.6	Improved
				CASES IN WHICH THE AVERAGE WAS OVER 2 MG. PER C.C.							
81	F	26	7 mos.	1.20	1.78	2.72	....	2.17	1.79	2.22	Recovered
82	F	62	16 mos.	1.02	1.90	2.42	....	2.27	1.58	2.09	Much improved
83	F	64	2½ yrs.	1.09	....	2.17	....	2.53	2.15	2.28	Much improved
84	F	22	6 wks.	1.00	....	2.60	....	2.90	2.10	2.53	Much improved
85	F	35	4 yrs.	1.2	....	2.4	....	2.5	1.5	2.1	No improvement
86	F	14	2 mos.	1.1	....	2.2	....	2.3	1.5	2.0	Recovered
87	F	55	4 yrs.	1.27	....	....	3.03	....	3.06	3.01	Improved
88	F	54	6 mos.	2.28	....	3.71	2.86	4.26	3.92	3.96	Much improved
89	F	52	8 mos.	1.78	....	3.17	....	2.59	1.97	2.57	Recovered
90	F	64	6 mos.	1.5	....	3.6	....	3.2	2.0	2.9	Much improved
91	F	..	.....	1.71	....	3.51	....	3.64	2.51	3.22	Much improved
92	F	52	4 yrs.	1.7	....	....	4.2	....	4.1	4.1	Much improved
93	F	61	10 yrs.	1.3	....	3.14	....	2.68	0.86	2.22	Much improved
94	M	45	18 mos.	2.2	....	4.5	....	4.6	3.8	4.3	Much improved
95	F	47	5 yrs.	1.3	....	2.6	....	3.0	1.9	2.5	Much improved
96	F	32	5 yrs.	1.0	....	3.47	....	....	2.75	3.11	Much improved
97	F	42	1 yr.	1.4	....	....	2.1	....	1.9	2.0	Much improved
98	M	57	4 mos.	1.1	....	4.2	....	1.4	0.67	2.06	Much improved
99	F	47	4 wks.	1.1	....	....	2.55	....	2.0	2.27	Much improved
100	F	27	1 yr.	1.34	....	3.70	....	3.30	3.10	3.37	No improvement

Group II and four to Group III. It may also be noted that there is no correlation between the figures obtained and the duration of the illness.

A division of the cases according to sex shows that in Group I fifteen are men and nine women; in Group II, twenty are men and thirty-six women; in Group III, two are men and eighteen women. The women, therefore, have a lower tolerance than the men.

An examination of the urine for sugar during the test was done in the earlier cases, but it was found that no glycosuria occurred, even when the blood sugar rose above 1.7 mg. per c.c. for a short time, and also the urine would show the absence of sugar throughout the test in cases showing a rise to 1.7 and remaining near this point for three hours. The examination of the urine following administration of sugar could not be used as a substitute for the blood sugar readings, and as it did not provide any additional information bearing on the point in question, the examination was not continued.

The Result of Dietetic Treatment.—The majority of the patients appeared to have received benefit by the treatment described. Of the

100 patients, eight recovered. These cases were necessarily of less severity than the average and had not gone on to permanent joint change. Forty-three were much improved, twenty-eight were improved and twenty-one showed no improvement. The improvement showed itself: (1) in the objective signs; (2) in relief from the pain and distress suffered by the patient, and (3) in improvement in the general health. In the twenty-eight patients grouped as improved, the result was largely subjective without much objective evidence of change in the joint. The forty-six who were much improved showed change on examination of the joint, as evidenced by decreased swelling, decreased limitation of movement and relief of muscle spasm. In some of these cases the improvement was immediate and striking, and no doubt could be entertained that it was the direct result of dietetic treatment. In two cases, a fall in temperature of 2 degrees (to normal) occurred within forty-eight hours of instituting treatment. As a rule, however, improvement set in slowly, starting in three or four days and being well marked in two or three weeks. After a month of treatment further progress was slow, but it was often marked enough to justify continuance of the diet for many months in favorable cases. Improvement in general health was generally a feature of the progress. Many of the patients suffered especially from some form of chronic dyspepsia, such as eructations of gas, loss or marked increase of appetite and abdominal distress. These symptoms, with very few exceptions, were very much relieved by the dietetic régimen, and sometimes entirely so. Constipation was present in the majority of the cases, often of a very obstinate form, and while at first this symptom might be aggravated somewhat, most patients at the end of their course of treatment would report at least considerable relief from this symptom. Three patients were relieved of chronic eczema. For the first week or two there was almost always some loss of weight. In a patient who was overweight this was desirable, and he was encouraged to reduce his weight further. Underweight was found to be no contraindication to the diet, for after a loss of from 5 to 10 pounds, no further loss was observed and sometimes the loss was followed by a gain to the original weight or even more. Patients who were underweight received as much benefit as did those who were overweight.

As to undesirable results of the treatment, one or two patients were unable to take milk and some other low diet was substituted. One patient had nausea and vomiting. This patient was found to have a heavy indicanuria and after a diet of vegetables, fruit and bread and butter for a week, he was able to continue with the program outlined. No other ill effects were observed as a result of the treatment.

These results are summarized in Table 2. A separate tabulation of the results with male and female cases shows that females are much more suitable for such treatment than males. The eight patients who recovered were women.

The Relationship of the Sugar Tolerance to the Effect of Reduction in Diet.—In those cases described as improved, the measure of improvement is largely dependent on the statement of the patient and is more or less an uncertain quantity. These cases, therefore, have been considered together with those unimproved for the purpose of demonstrating this relationship. The recovered cases are considered with those much improved, as these cases showed definite objective changes as a result of the treatment. The results are shown in Table 3.

TABLE 2.—SUMMARY OF THE RESULTS OF DIETETIC TREATMENT

	Total	Male	Female
Recovered	8	0	8
Much improved	43	14	29
Improved	28	10	18
Not improved	21	13	8
	100	37	63

TABLE 3.—THE EFFECTS OF TREATMENT ON CASES GROUPED ACCORDING TO THE SUGAR TOLERANCE

	Average Blood Sugar Reading for Three Hours		
	Less than 1.4	1.4 to 2	More than 2
Recovery or showing objective improvement	3 (12.5%)	31 (55.3%)	17 (85%)
No objective improvement	21 (87.5%)	25 (44.7%)	3 (15%)

TABLE 4.—ANALYSIS OF CASES ON BASIS OF SEX

	Less than 1.4		1.4 to 2		More than 2	
	Men	Women	Men	Women	Men	Women
Recovery or showing objective improvement	0	3	12	19	2	15
No objective improvement	15	6	8	17	0	2

Table 4 shows a similar relationship of the results on the sugar tolerance when the male and female cases are separately analyzed.

These figures show that the response to reduction of diet in an arthritic is roughly proportionate to the reduction of the sugar tolerance. This relationship, however, is not without quite evident exceptions. Case 100, with an average over 3.3, was a well nourished woman without evidence of any focus of infection which might interfere with progress, yet no effect of any sort was observed as a result of the treatment, and after six weeks she gave it up. In Cases 85 and 87 some relief of symptoms was apparent without any objective change. Both patients, however, were sufficiently impressed with the value of

the treatment to continue with the diet for several months. One patient (Case 8), who had an almost normal tolerance, showed immediate improvement and has had no relapse after eighteen months. Cases 15 and 24 showed some improvement on examination, but this progress, however, was quite less than the average result. These cases, however, were decidedly the exceptions and it is felt that in a case with a low tolerance one is able to offer, with confidence, a good prospect of improvement; while, on the other hand, a case with normal tolerance seldom showed progress enough to encourage one to recommend this form of treatment as a routine procedure.

DISCUSSION

Many of the factors exerting an influence on sugar metabolism are still somewhat obscure, and the clinical significance of the glucose tolerance test is as yet uncertain. The test was originally introduced with the object of detecting the potential diabetic but the occurrence of a low tolerance in other conditions has rendered its use for this purpose somewhat unreliable when considered by itself. A low tolerance has also been accepted as evidence of some endocrine unbalance but its value here is as yet unproved. There is some evidence to suggest that a disturbance of the sugar tolerance is associated with infections, as suggested by Pemberton and Foster [2] and also by the studies of F. M. Allen [6] and others on diabetics. Our own experience would bear this out. In one case a slightly lowered tolerance was converted into a very much lowered tolerance by the operation of tonsillectomy, and for three weeks the blood sugar remained above 3 for the three hours of the tolerance test. After four weeks the tolerance test returned to the original reaction. It is our opinion that this temporary disturbance of sugar tolerance was due to a lighting up of the infection at the site of the operation. As a general rule, the tolerance is increased by removal of foci of infection. It is reasonable then, to account for the lowering of tolerance in arthritis by the presence of an infection, and Pemberton suggests that the rationale of his dietetic treatment is that he is catering to a function weakened by infection. But, on the face of it, it is difficult to believe that in some of the milder causes of Group III such a disturbance in sugar metabolism could be brought about by the arthritic infection alone.

If the lowering of the tolerance is not the result of the disease process, it is quite possible that it is associated with the pathogenesis of arthritis. Clinical observation would seem to offer some support of this hypothesis. In one case we were able to produce an acute exacerbation of the disease by allowing carbohydrates freely; this was

6. Allen, F. M.: Unpublished Studies on Diabetes quoted by Sherrill, J. W., J. A. M. A. **77**:23 (Dec. 3) 1921.

done three times in the same case. Pemberton brought about a similar relapse in one of his cases in the same way. When the former diet of the patients is scrutinized, it is often found to have been unbalanced, especially in excess of carbohydrate food, and the frequency of this observation is such as to suggest that it should be considered as a possible cause of the condition. And, lastly, the results of treatment in the present series of cases would appear to have an important bearing on this point. No explanation is sufficient which suggests that the treatment is directed simply toward the relief of some secondary process, for sometimes the response is so marked and so striking that one is convinced that the diet must be closely related to the origin of the disease, and the relationship of the sugar tolerance to these results would indicate that this origin is intimately connected in some way with the metabolism of carbohydrates.

Further discussion of this subject may be speculative, but, perhaps, one or two more points may be brought up. When various low diets were being tried, it was found that reduction of carbohydrates alone did not yield the best results, and the diet finally chosen was one which was not only low in calories but which was rich in vitamin content. Results with this diet appeared to be favorable enough to suggest the existense of an actual vitamin deficiency. Others, notably Thompson,[7] have emphasized the importance of these accessory food factors in the diet of arthritics. The addition, however, to the patient's former diet of food rich in vitamin was by no means as effective as the combination of vitamins with a subcaloric diet, as described, and if a vitamin deficiency exists in those cases which received benefit by reduction of carbohydrates, it is likely that carbohydrates play some part in the production of this deficiency. McCarrison[8] and Mellanby[9] have found that carbohydrate excess is an important factor in deficiency disease, and Funk[10] associates vitamin B with carbohydrate metabolism—reporting a hyperglycemia in beriberi. Findlay, Paton and Sharpe[11] found a decreased sugar tolerance in a case of rickets. McCarrison further believes that excess of fats as well as carbohydrates must be considered in the production of deficiency disease. This fits in well with our own observations on the dietetic treatment of the arthritics who were overweight. For in these cases, reduction of fat has always appeared beneficial, and, while reduction of fat has not been urged in

7. Thompson, F. G.: Dietetics in Chronic Arthritis, Practitioner **103**:110 (Aug.) 1919.

8. McCarrison, R.: Studies in Deficiency Disease, London, 1921.

9. Mellanby, E.: Accessory Food Factors in Feeding of Infants, Lancet **1**:856 (April 17) 1920.

10. Funk, C.: Action of Substances Influencing Carbohydrate Metabolism in Experimental Beri Beri, J. Phyiol. **53**:247 (Dec.) 1919.

11. Findlay, L., Paton, D. N., and Sharpe, J. S.: Studies in Metabolism of Rickets, Quart. J. Med. **14**:352 (July) 1921.

those underweight, it has been given in the form of cod liver oil and cream in moderation. Such a deficiency would also account for the relationship of diet with what appears to be a infectious disease, for it has been repeatedly found, as pointed out by McCarrison [8] and Hess [12] that infections readily light up in deficiently fed animals.

If, then, excess of the energy bearing constitutents of the food may induce deficiency disease, especially in the presence of inadequate vitamins and protein, and if infections are liable to appear before actual deficiency syndromes develop, it is a fair hypothesis that in the presence of some focus of infection lack of balance in the diet is a cause of chronic arthritis in a large number of cases, and that the results reported in this paper are due to measures directed toward the correction of this defect.

These considerations are presented with the full appreciation of the fact that one phase only of the treatment has been dealt with. If diet is a factor in the etiology of this disease, there are likely many others, as, foci of infection, exposure, fatigue and other disease. Influenza was the exciting cause in many of the cases studied, and these cases were sometimes among those most favorably influenced by diet. It is interesting to note that a low sugar tolerance may follow this disease (Cowie and Beavan [13]).

No special observations are included as to the value of other therapy for the object of the investigation was to study the value of diet alone, but after this had been observed, it was found worth while to institute other forms of treatment, especially hydrotherapy and physiotherapy. Foci of infection, when of considerable size, appeared to interfere with the favorable effects of diet, and it is recommended that these should always be looked for and, if possible, removed before dietetic treatment is started. One patient, however, recovered in spite of the existence of several abscesses at the roots of the teeth, which the patient had refused to have extracted. But such infectious foci were found only in a minority of the cases, and when removed none of the effects reported here could be attributed to this procedure.

The more favorable results, along with the considerably lower tolerance in women, might call for some comment. This might be associated with some fundamental difference in their metabolism, to their manner of living, or, perhaps, to their dietetic habits. Certainly, lack of balance in diet is more frequently found among women than among men, especially carbohydrate excess, with an inadequacy of protein. In this connection, it might be mentioned that reduction of protein in chronic arthritis, as is so often practised, appears to be productive of much harm.

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12. Hess, A. F.: Newer Aspects of Some Nutritional Disorders, J. A. M. A. **76**:693 (March 12) 1921.
13. Cowie, D. M., and Beavan, P. W.: Arch. Int. Med. **24**:78 (July) 1919.

CONCLUSIONS

1. Of 100 cases of chronic arthritis, reduction of diet alone appeared to result in the recovery of eight patients and in quite evident improvement in forty-three.

2. The sugar tolerance was decreased in the large majority of these cases, and this decrease showed no relationship to the severity of the disease.

3. Patients who have a low tolerance are much more frequently benefited by reduction in diet than those cases with a normal tolerance.

4. In certain cases of chronic arthritis, dietetic regulation appears to be the most effective form of treatment, and while the value of such treatment in an individual case cannot be determined with certainty, the lowering of the sugar tolerance is a useful clinical indication for this procedure.

5. Female patients derive greater benefit from such treatment than men, and, as a rule, they show a lower tolerance.

VARIATIONS IN ALIQUOT FRACTIONS OF GASTRIC CONTENTS*

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In a previous paper [1] attention has been directed to the fact that single determinations of gastric acidity by the Rehfuss method are not sufficient on which to base conclusions, because they do not take into account individual variation. Another important question which arises in evaluating results obtained by this method is whether the aliquot fractions aspirated are truly representative of the total gastric contents at the time of withdrawal. Recently, Gorham [2] has shown that "the gastric chyme is not, in the majority of instances, a homogeneous mixture after a test meal, and that the acidity of different portions may vary widely." He found on the withdrawal in rapid succession of many samples that there was a marked variation in acidity of these samples in subjects having clinical evidence of gastric disease. Such variations were not so apparent in subjects without clinical evidence of gastric disease, although Wheelon [3] has reported some interesting variations in normal subjects.

PART I

In view of the important bearing of this observation on the errors involved in the Rehfuss fractional method of gastric analysis,[4] the following experiment was conducted. A group of subjects showing no clinical evidence of gastric disease were given the standard Ewald meal after removal of the fasting contents. No further samples were aspirated until three-quarters of an hour had elapsed, whereupon the entire gastric contents were removed as rapidly as possible by the successive withdrawal of 10 c.c. samples. This procedure usually required ten or fifteen minutes. The acidity of the samples was then determined in the usual manner by the titration and colorimetric methods.[1] The results are presented in Figures 1, 2, 3, 4, 5, 6 and 7. Figures 1 to 5 represent the graphs of psychotic subjects, while Figures 6 and 7 are of normal individuals.

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* Read at Society for Experimental Biology and Medicine, Jan. 18, 1922.

* From the Department of Bacteriology, Psychiatric Institute of the New York State Hospitals, Ward's Island.

1. Kopeloff, N.: Individual Variation as Influencing the Rehfuss Fractional Method of Gastric Analysis, J. A. M. A. **78**:404 (Feb. 11) 1922.

2. Gorham, F. D.: Variations of Acid Concentration in Different Portions of the Gastric Chyme, and Its Relation to Clinical Methods of Gastric Analysis, Arch. Int. Med. **27**:434 (April) 1921.

3. Wheelon, H.: Relation of the Gastric Content to the Secretory and Motor Functions of the Stomach, Arch. Int. Med. **28**:613 (Nov. 15) 1921.

4. Editorial: Critique of Gastric Analysis, J. A. M. A. **77**:202 (July 16) 1921.

TABLE 1.—VARIATION IN 10 C.C. FRACTIONS REMOVED IN RAPID SUCCESSION BY THE REHFUSS TUBE THREE QUARTERS OF AN HOUR AFTER THE MEAL

Patient	Number Samples	C.c. N/10 NaOH High Pt.	C.c. N/10 NaOH Low Pt.	Average	Average Deviation
M. Hr.	7	94	11	38	±18.0
M. Kn.	7	82	41	62	±11.5
M. By.	10	74	41	56	± 8.0
I. Sn.	14	51	33	43	± 3.5
E. Kg.	5	41	28	35	± 5.0
Normal Controls:					
M Ma.	14	63	35	51	± 7.0
C. Te.	9	69	58	64	± 3.0

The data have been further summarized in Table 1. It is evident that there is a wide variation in the acidity of successive samples taken from the same individual. For example, in the first subject (M. Hr.) the variation between the high point (94) and the low point (11) is 83. Such a striking divergence means that there is a gross error involved

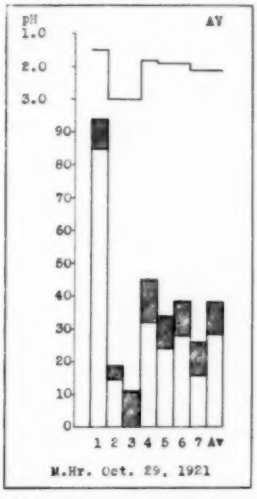

Fig. 1.—The ordinates 0-90 represent cubic centimeters of tenth normal sodium hydroxid per 100 c.c. of gastric contents; p_H, from 1.0 to 3.0: the hydrogen-ion concentration measured colorimetrically. The abcissae represent the number of samples taken; with the final column as an average of the preceding acidities. The colorless portion of each column represents the free acidity, while the light and the shaded portions together represent the total acidity.

in assuming any single sample as being representative of the total gastric contents. The last column marked "average deviation" brings this out mathematically. The average deviation is calculated in the following manner. The individual readings, such as 94, 19, 11, 45, 34, 38 and 26, are averaged, giving a mean of 38. The first reading (94)

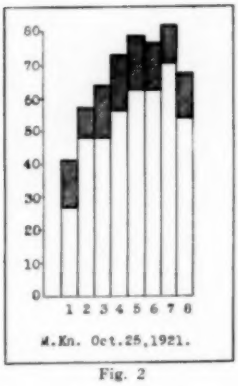

Fig. 2

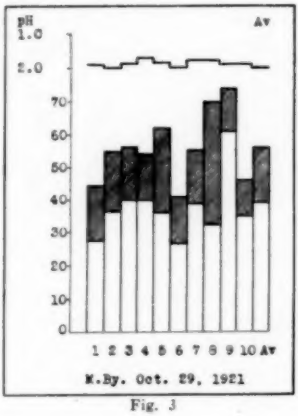

Fig. 3

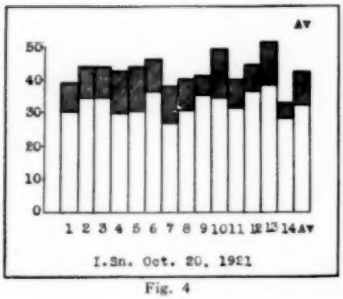

Fig. 4

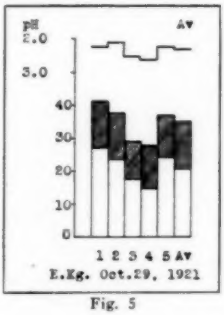

Fig. 5

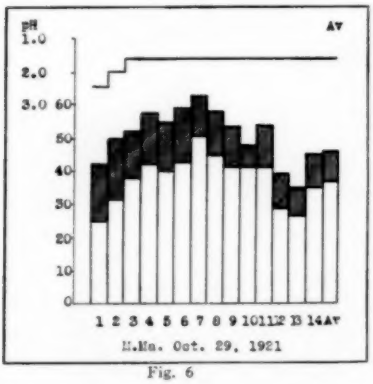

Fig. 6

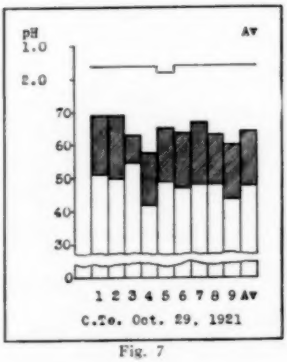

Fig. 7

deviates from the mean by 56; the second reading deviates by 19, and the third by 27—and so on. The sum of these deviations is 131. Dividing by the number of instances (7) one obtains the average deviation, which is ± 18. In other words, considering the first subject, any single sample might be 18 more or 18 less than the average of all samples—which is virtually a range of uncertainty amounting to 36. Obviously, comparisons or conclusions based on such an uncertain method, when the experimental error is not calculated or taken cognizance of, are open to severe criticism.

It is scarcely necessary to discuss in detail the results obtained with the other subjects, for they merely emphasize in varying degree the points already established. Suffice it to say, that there was little difference between the normal controls and the psychotic patients having a similar acidity. In other words, it seems to be generally true that in subjects showing a fairly high gastric acidity one is more likely to find wider fluctuations than in those having a lower acidity. This may, perhaps, account for Gorham's findings, namely, that subjects with evidence of clinical disease, show wider fluctuations than the normal; and one may really expect that individuals without clinical evidence of disease who have a high acidity will also exhibit wide variations.

PART II

The above experiment explains, in part, the great variety of acidity curves obtainable by the fractional method of gastric analysis, and the fundamental errors involved in single determinations. The fraction obtained at any one moment cannot, therefore, be accepted as representative of the total gastric contents, for it is entirely dependent on the position of the tip of the tube in the stomach at the moment of withdrawal. Obviously, this position "is necessarily a constantly changing one, due, first, to the change of size and position of the stomach while emptying itself through the pylorus, and by aspiration; second, the shortening and lengthening of the stomach from gastric contraction; third, the peristaltic waves that tend to carry the tube toward the pylorus." [2] The experiment described in Part 1, indicates that the gastric contents are not homogeneous, but the method involved is open to criticism on the ground that some little time is required to rapidly withdraw the successive samples, and that during such lapse of time the gastric acidity might actually be undergoing change. The following experiment, therefore, was designed not only to yield definite information concerning the acidity in different parts of the stomach at the same moment, but also to eliminate the lapse of time required in withdrawing several samples. The following procedure was carried out on three subjects, two psychotic patients and a normal individual. A Rehfuss tube was inserted to a depth of 50 cm. (measured from the teeth).

Then a second Rehfuss tube was inserted to a depth of 45 cm.; and, finally, a third Rehfuss tube was inserted to a depth of 40 cm. The gastric contents of each subject were removed simultaneously through all three tubes, by having the operators aspirate the contents at the same moment. The tubes were labeled and special care was taken to have each tube at the proper level before any gastric contents were removed. The standard Ewald meal was given and as usual, at fifteen minute intervals, samples were withdrawn, except that during these fractional analyses, three samples were aspirated simultaneously at the designated time. At the end of the analyses, each subject was given a glass of milk containing a small amount of bismuth subnitrate (15 grains) and a roentgenogram was taken to determine the relative posi-

TABLE 2.—VARIATION IN ACIDITY OF THREE ALIQUOT FRACTIONS OF GASTRIC CONTENTS WITHDRAWN SIMULTANEOUSLY (M. MCA.)

Time, Hours	Total Acid	Average ± Average Deviation	Free Acid	Average ± Average Deviation	pH	Average ± Average Deviation
F. C.	45		33		1.6	
	22	34 ± 12	9	21 ± 12	1.6	1.6 ± 0
¼	22		12		3.4	
	30		18		2.5	
	7	20 ± 8	0	10 ± 7	5.4	3.8 ± 1.1
½	39		18		3.0	
	39		27		2.9	
	22	33 ± 8	14	20 ± 5	2.9	2.9 ± 0
¾	69		38		2.2	
	56		30		2.4	
	28	51 ± 15	18	29 ± 7	2.1	2.2 ± 0.1
1	74		51		1.7	
	63		42		...	
	21	53 ± 21	14	36 ± 14	2.5	2.1 ± 0.4
1¼	73		49		1.8	
	68		46		...	
	37	59 ± 15	29	41 ± 8	1.8	1.8 ± 0
1½	47		35		2.1	
	63		42		1.8	
	36	49 ± 10	22	33 ± 7	2.1	2.0 ± 0.1
1¾	42		28		2.1	
	43		29		1.9	
	8	31 ± 15	0	19 ± 12	4.5	2.8 ± 1.1
2	35		22		1.9	
	27	31 ± 4	19	21 ± 1	2.0	2.0 ± 0

tions of the Rehfuss tubes maintained at a constant level. The acidity of the samples was determined in the usual manner by titration and colorimetric methods. The results of total acidity are graphically presented in Figures 8, 9 and 10, and summarized in Tables 2, 3 and 4.

In Table 2, may be found several points of interest. Chief among these are the wide variations occurring in the total or free acidity of the three fractions aspirated at any one time. Glancing down the second column marked "total acid" it is seen that at the one hour period there is a variation from 21 to 74, or an actual difference of 53. This is, perhaps, larger than the differences found at other periods, but since the one hour period is ordinarily of special interest, these figures are significant. In the third column is given the average of the three

TABLE 3.—Variation in Acidity of Three Aliquot Fractions of Gastric Contents Withdrawn Simultaneously (M. Hr.)

Time, Hours	Total Acid	Average ± Average Deviation	Free Acid	Average ± Average Deviation	p_H	Average ± Average Deviation
F. C.	19		5		5.0	
	25	22 ± 3	11	8 ± 3	4.0	4.5 ± 0.5
¼	17		13		...	
	25		15		3.0	
	22	21 ± 3	10	13 ± 2	3.0	3.0 ± 0
½	42		26		2.3	
	40		29		2.3	
	41	41 ± 1	31	29 ± 2	2.1	2.2 ± 0.1
¾	61		44		2.1	
	72		54		1.8	
	56	63 ± 6	43	47 ± 5	1.7	1.9 ± 0.2
1	70		48		1.9	
	82		66		1.6	
	65	72 ± 6	51	55 ± 7	1.6	1.7 ± 0.1
1¼	79		60		1.7	
	71		56		1.7	
	62	71 ± 6	48	55 ± 4	1.7	1.7 ± 0
1½	65		56		1.7	
	65		53		1.6	
	48	59 ± 7	38	49 ± 7	1.7	1.7 ± 0
1¾	80		71		...	
	58		47		1.7	
	51	63 ± 11	43	54 ± 12	1.7	1.7 ± 0
2	74		64		1.6	
	61		53		1.6	
	61	65 ± 6	54	57 ± 5	1.7	1.6 ± 0

TABLE 4.—Variation in Acidity of Three Aliquot Fractions of Gastric Contents Withdrawn Simultaneously (M. By.)

Time, Hours	Total Acid	Average ± Average Deviation	Free Acid	Average ± Average Deviation	p_H	Average ± Average Deviation
F. C.	58		43		1.6	
	53		41		1.6	
	7	38 ± 20	0	28 ± 19	4.5	2.6 ± 1.3
¼	32		27		2.1	
	32		23		1.9	
	18	27 ± 6	13	21 ± 5	3.4	2.5 ± 0.6
½	50		33		1.9	
	32		19		2.4	
	18	33 ± 11	8	20 ± 9	3.5	2.6 ± 0.6
¾	66		49		1.7	
	67		51		1.7	
	28	54 ± 17	19	40 ± 14	3.0	2.1 ± 0.6
1	70		60		1.6	
	78		68		1.5	
	59	69 ± 7	44	56 ± 8	1.7	1.6 ± 0.1
1¼	78		64		1.6	
	82		78		1.6	
	75	75 ± 3	57	65 ± 6	1.6	1.6 ± 0
1½	79		64		1.6	
	79		62		1.6	
	61	73 ± 8	44	57 ± 8	1.6	1.6 ± 0
1¾	75		61		1.6	
	78		66		1.6	
	51	68 ± 11	37	55 ± 12	1.6	1.6 ± 0

fractions with the calculated average deviation. This shows conclusively how large the margin of uncertainty actually is, if one assumes any single reading as representative of the total gastric contents at any particular moment.

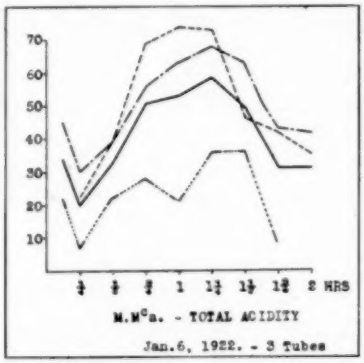

Fig. 8.—The ordinates 0-90 represent cubic centimeters of tenth normal sodium hydroxid per 100 c.c. of gastric contents; P_H from 1.0 to 3.0: the hydrogen ion concentration measured colorimetrically. The abcissae represent quarter hour intervals, and F. C.=fasting contents. The broken line represents the fraction taken from the tube at 50 cm.; the dash and dot alternately, represents the fraction taken from the tube at 45 cm.; the dash and several dots alternately, represents the fraction taken from the tube at 40 cm.; while the solid line represents the average of the three fractions taken.

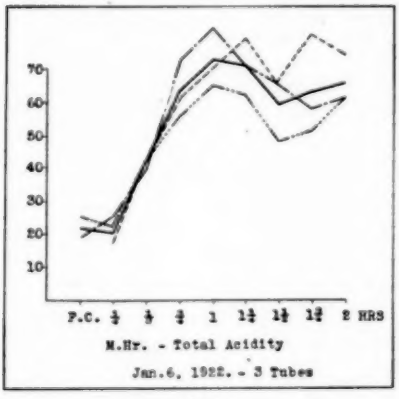

Fig. 9

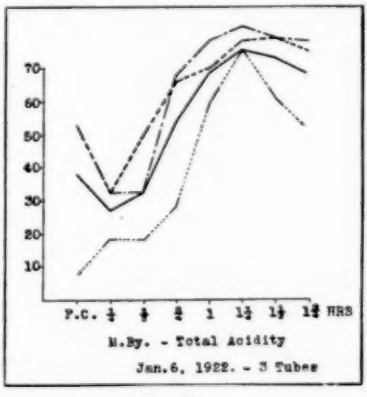

Fig. 10

Figure 11 brings this point out even more strikingly. Usually, the higher the acidity, the wider the margin of uncertainty—a generalization already referred to in Part I. It is apparent from this graph that curves of various kinds could be drawn within the shaded area, from one designated by Rehfuss isosecretory to one designated hyposecretory.

This substantiates my earlier contention that a single determination by the Rehfuss fractional method of gastric analysis is not sufficiently valid on which to base a conclusion.[1] It is clearly shown in the data here presented, that fractions taken from different parts of the stomach are not homogeneous in character, but differ widely in acidity. The roentgenograms indicate the relative position of the tubes during the analyses. One of these is shown in Figure 12.

As might be expected, the free acidity values in Table 2, in general, run parallel to those obtained for total acidity. But it is noteworthy that this does not hold true for p_H. Here there is much closer agreement between the three fractions than when acidity is measured by titration. This means that the buffer salts are of paramount importance in the measurement of true gastric acidity. This lends further emphasis

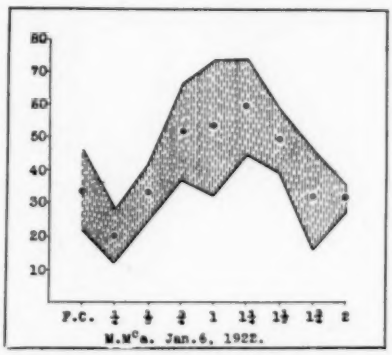

Fig. 11.—The points in circles in the shaded area represent the average of the three fractions at the time indicated on the abcissae, while the shaded area above and below each point indicates the possible range into which the reading at that moment might fall.

to the valuable work of Shohl [5] and shows how misleading an index of gastric acidity a single titration may be.

The other tables bring out in varying degree the facts already referred to and do not require a repetition of the discussion. It is of interest, however, to note that the normal individual (M. McA.) exhibited even wider fluctuations in three fractions aspirated at the same time, than the two psychotic subjects (M. Hr. and M. By.), so that it cannot be said that the mental status has any particular bearing on the point at issue. Naturally, various individuals would be expected to differ with regard to the homogeneity of their gastric contents; nevertheless, this experiment indicates that it is erroneous to assume that any such homegeneity exists.

5. Shohl, A. T.: Determination of the Acidity of Gastric Contents, Johns Hopkins Hosp. Bull. **31**:152 (May) 1920.

In Tables 2, 3 and 4, a rather interesting phenomenon obtains. The fraction taken from the tube inserted at 40 cm. is almost invariably lower in total and free acidity than the fractions taken at a depth of 45 or 50 cm. Furthermore, these samples were totally different in physical character—being of a much lighter color often, water-white, and containing lesser amounts of starch. This is to be expected from the work of Prym [6] and Sick,[7] who have shown that the acidity of the pyloric gastric contents varies considerably from the fundal portion, but their methods are not as conclusive as the one herein described, since

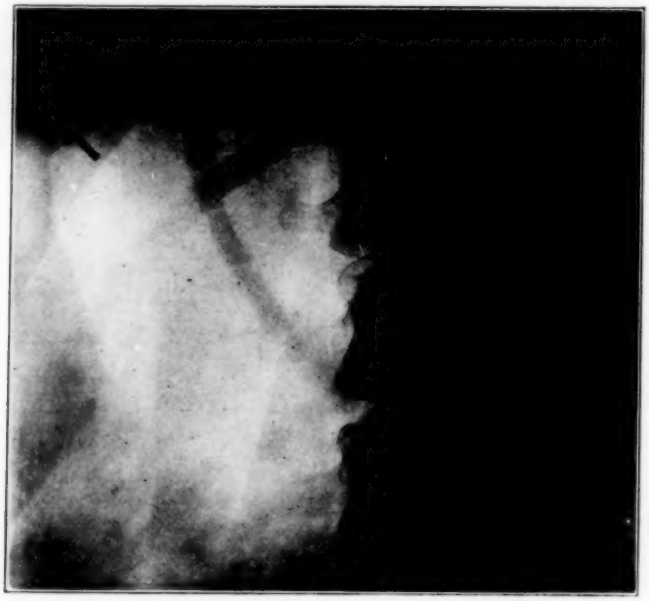

Fig. 12.—Relative position of Rehfuss tubes during fractional analysis with three tubes.

they did not use more than one tube. Very little difference was found between fractions obtained at 45 and 50 cm., respectively. However, the fact that these two fractions are usually in close agreement indicates that in that region the stomach contents were, perhaps, of a more homogeneous character. In plotting the curves of the fractions taken at each level, a certain general similarity may be noted, despite the recrossing at numerous points. This might seem to indicate that if the level of the tube were kept constant, single determinations might yield a characteristic curve. However, the errors are too fundamental

6. Prym: Deutsch. Arch. f. klin. Med. **90**:310 (June) 1907.
7. Sick: Deutsch. Arch. f. klin. Med. **88**:169 (Oct.) 1906.

to be thus lightly disregarded. For despite the similarity in curves, each curve has its peculiar margin of uncertainty, and thus the possibility of obtaining the characteristic curve would be seriously diminished. In other words, an average deviation of ± 12 for every sample, or practically 25 c.c., in the first subject, implies a wide margin of uncertainty.

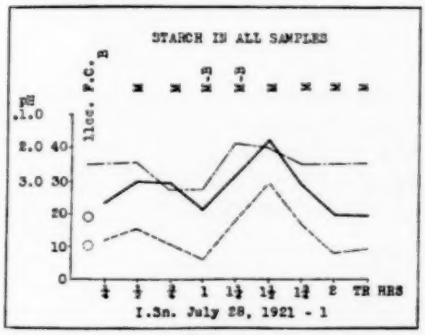

Fig. 13

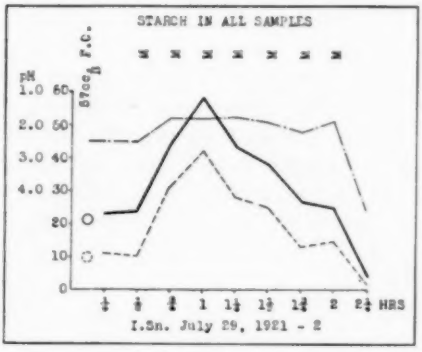

Fig. 14

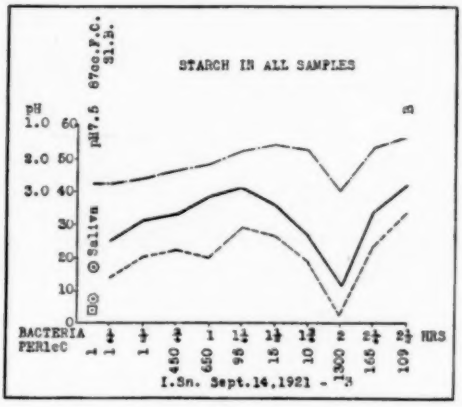

Fig. 15

Figs. 13, 14 and 15.—Fractional analysis of stomach contents of a natural regurgitator.

PART III

The problem of determining whether or not a small aliquot is truly representative of the total gastric contents was approached from still another aspect. Through the kindness of Dr. William C. Garvin, superintendent of Kings Park State Hospital, there was transferred to Ward's Island a psychotic patient who could be called "a natural regurgitator," i. e., one who could deliver his total gastric contents

at will, or on very slight stimulation of the palate. This patient gave a history of frequent vomiting after meals for which no adequate explanation could be given other than that it was an hysterical symptom. Since admission to Manhattan State Hospital, the vomiting has become relatively infrequent and generally occurs only after the patient has been visited. Several fractional gastric analyses were performed on him in the usual way (Figs. 13, 14 and 15). Other than the relatively low acidity, there is little that is worthy of comment in Figures 13 and 15; while in Figure 14, the curve is typically isosecretory.

The power to regurgitate at will was utilized to study the homogeneity of the gastric contents. The subject was given the standard Ewald meal on several different days and instead of removing the contents by the fractional method, the total gastric contents were regurgitated on the first day after one-quarter hour, the next day after one-half hour, and so on, in such a way as to make it possible to plot a

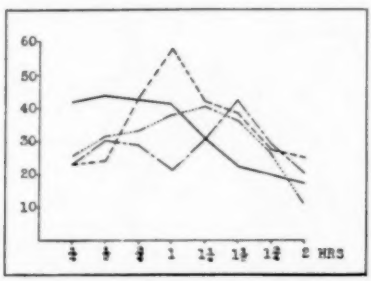

Fig. 16.—Homogeneity of gastric contents. Only the total acidity is shown. The solid line represents the total contents. The broken lines represent the fractional contents.

curve over the two-hour period, similar in scope to the usual fifteen minute fractions taken on the same day. A comparison of this curve with those obtained by the usual method is presented in Figure 16.

This curve representing the acidity of the total gastric contents has a higher initial acidity and a lower final acidity than that ordinarily found. Furthermore, instead of showing a gradual rise and decline, it is decidedly atypical in starting high and declining steadily. These peculiarities can scarcely be ascribed to the lapse of time between analyses, since the usual fractional method conducted at about the same intervals showed no marked changes, and the patient remained in about the same physical and mental condition so far as could be ascertained. While this method of conducting a gastric analysis is unusual, it gives a more adequate picture of the subject's gastric cycle of digestion than the routine method in vogue. Gorham [2] states that "the true fractional analysis necessitates the giving of successive test meals and extracting them at different periods."

A feature of some importance was added to the procedure described above, namely, an aliquot sample of 10 c.c. was taken by means of the Rehfuss tube immediately prior to the regurgitation of the total gastric contents; in fact, the removal of the Rehfuss tube in these instances stimulated "natural regurgitation." The comparison of each aliquot with the corresponding total contents is given in Table 5.

In a subject having a rather low gastric acidity, as has already been pointed out, large differences could not be expected. However, it is significant that there are noticeable differences. This fact, together with the others mentioned in Parts 1 and 2, serves to complete the evidence against the usual technic of the Rehfuss method in which it is assumed that the aliquot withdrawn is representative of the total gastric contents, showing that such an assumption has little basis in fact.

While these experiments may appear to be entirely destructive in character, nevertheless, certain constructive points have been estab-

TABLE 5.—Comparison of Aliquot with Corresponding Total Gastric Contents Obtained by "Natural Regurgitation"

Time	Total Acidity in C.c. N/10 NaOH	
	Aliquot	Total Contents
1 hour	49	41
1½ hours	37	22*
2 hours	22	17

* Some bile present.

lished. First and foremost, in using the Rehfuss method, it is essential to repeat the analysis until a satisfactory agreement in curves is obtained. Second, the tube should be kept at a constant level. This can easily be accomplished by fastening the tube to the cheek by means of a strip of surgeon's adhesive tape. Third, the aliquot fractions should be as large as possible. Fourth, the subject should expectorate freely, swallowing as little saliva as possible. Finally, the acidity should be measured in terms of hydrogen ion and buffer salts, and not by the inaccurate titration method in common usage.

SUMMARY

1. A wide variation was found in the acidity of 10 c.c. fractions withdrawn in rapid succession by means of the Rehfuss tube three-quarters of an hour after the test meal was ingested. This was more noticeable in subjects having high rather than low gastric acidity.

2. By inserting three Rehfuss tubes in one individual and aspirating the fractions simultaneously at fifteen minute intervals, it was found that there was considerable variation of acidity in different parts of the stomach at the same moment. Roentgenograms established the relative position of the tubes.

3. From these data it is shown that widely divergent curves of acidity may be plotted which depend entirely on the experimental error of the method and not on the subject's gastric condition.

4. The inadequacy of the titration method and the importance of hydrogen ions and buffer salts in measuring gastric acidity is indicated.

5. By comparing the periodic "natural regurgitation" of total gastric contents with the fractions ordinarily obtained by the Rehfuss method, discrepancies are noted.

6. Results obtained by the Rehfuss method may be more validly interpreted if: (a) the analysis is repeated until a satisfactory agreement in curves is obtained; (b) the tube is kept at a constant level; (c) aliquot fractions are large; (d) little saliva is swallowed; (e) acidity is measured in terms of hydrogen ion and buffer salts.

CONCLUSION

Aliquot fractions obtained by the Rehfuss method of gastric analysis cannot be assumed to represent accurately the total gastric contents.

I am indebted to the individuals who made these experiments possible and to the members of the staff for their generous assistance. Particular thanks are due Dr. C. O. Cheney for his many valuable suggestions and help on the wards, and to Mr. E. J. Kennedy for his efficient and painstaking work in the laboratory.

BOOK REVIEWS

HAY FEVER AND ASTHMA. WILLIAM SCHEPPEGRELL. Philadelphia and New York: Lea & Febiger, 1922.

This text, pleasingly concise, presents the etiologic relationship of plant pollen to hay-fever, and mentions for each state of the United States the particular plant pollen seasonally associated with hay-fever. Although the title implies a discussion of asthma, very little mention of this disease is made in the text. The preventive control of hay-fever, and its treatment are presented adequately. The book is a useful guide in determining the offending pollen, and in the treatment of hay-fever patients.

MANUAL OF CLINICAL LABORATORY METHODS. C. L. CUMMER. Philadelphia and New York: Lea & Febiger, 1922.

This is a convenient laboratory manual, systematically presented, and adequately describes the present methods essential for good clinical laboratory work. That portion of the text concerned with the blood includes directions for the usual cytologic examinations, serologic and bacteriologic tests, and also for the quantitative estimation of many of the chemical substances of the blood, such as sugar, urea, total nonprotein nitrogen, creatinin, uric acid, alkaline reserve, chlorids, and oxygen. There are chapters describing the methods for urine analysis, the examination of gastric and duodenal contents, of feces, sputum, body fluids, and also for bacteriologic examinations. This book meets the needs of any clinical laboratory worker, and of physicians who desire interpretation of laboratory reports.

BACTERIOLOGY: GENERAL PATHOLOGICAL; INTESTINAL. A. I. KENDALL. Philadelphia and New York: Lea & Febiger, 1921.

Kendall's revised bacteriology (Ed. 2) needs little introduction as a reference text to advanced students of bacteriology. As a text for courses in bacteriology to medical students and to students of general bacteriology, it deserves favorable consideration. The revision has brought into the text discussion of certain pathogenic bacteria which during the war became especially important. Entire sections of the book are rewritten and extensive changes or additions made to nearly every chapter. A section discussing gastro-intestinal bacteriology is a distinctive feature of this book.

THE VITAMINS. By H. C. SHERMAN, Professor of Food Chemistry, Columbia University; and S. L. SMITH, Specialist in Biological and Food Chemistry, U. S. Department of Agriculture. New York: The Chemical Catalog Company, 1922.

This book combines scientific accuracy with simple diction, so that it can be studied with ease and profit by the educated layman and by the doctor who left school before the recent discoveries in the vitamin field of nutrition. The first chapter contains an excellent historical review of the development of knowledge of the vitamins and their rôle in health and disease. The following three chapters deal in detail with the antineuritic, the antiscorbutic, and the fat soluble vitamins, respectively. The final chapter deals with the very important subject of vitamins in our ordinary foods. There are good subject and authors' indexes, and a bibliography of 1,000 titles, for those who have the time and the inclination to consult the original publications. The authors are men of recognized attainment in the field of food and nutrition.

The book is one of the best, if not the best, written on the timely subject of the vitamins. It will help to allay the hysteria that now threatens to develop on the subject of the vitamins and vitamin deficiency diseases, a hysteria brought on by baseless claims of vitamin deficiency in our common food, and generously nursed by vitamin proprietary purveyors.

NERVE EXHAUSTION. By MAURICE CRAIG, C.B.E., M.D. (CANTAB.), F.R.C.P. (LOND.), Physician for and Lecturer in Psychological Medicine, Guy's Hospital. Late Examiner in Diploma for Psychological Medicine, Cambridge University. 148 pages. Philadelphia, Lea & Febiger. 1922.

The outstanding features of this book are common sense and simplicity. In spite of his undoubted possession of perfect knowledge of modern psychopathologic lingo, the author expresses his ideas in plain English, even avoiding such terms as neurasthenia and psychasthenia. Nerve exhaustion is discussed under five principal headings: causation, symptomatology, sleeplessness, diagnosis and prognosis, treatment. According to Craig, there is nothing haphazard about fatigue and it is our duty to discover the rules governing its occurrence. His discussion of the hypersensitive, precarious child and its management if read not only by physicians, but by teachers and educated parents would be most helpful in the prevention of nervous invalidism. His ideas on gastro-intestinal hygiene may sound a little revolutionary to most Americans with whom "regulation" of the bowels has almost become a national duty. We are told that a tendency to looseness of the bowels is much more harmful to the nervous system than constipation. He does admit that "colitis" is usually associated with constipation, but adds that it is common in highly-strung persons and that "it is wise to focus the treatment as little as possible upon the condition, as the psychical effect of doing so may be both great and lasting." In commenting on the comparative frequency of nervous exhaustion following surgical operations he deplores the tendency to unnecessarily violent purging just before operations. The author evidently has carefully studied the Freudian Philosophy—and finds it wanting. He does not believe that sexual conflicts and suppressions are of necessity the cause of psychoneuroses. He is also impressed with the harm frequently done to patients by psychoanalytic treatment. Altogether we can heartily recommend this book to physicians no matter what line of work they may follow, as it will enable them to understand better the one subject common to general practitioners and specialists alike—the patient himself.